Exhibit 11

US006036631A

United States Patent [19]

McGrath et al.

[11] Patent Number: 6,036,631

[45] Date of Patent: Mar. 14, 2000

[54] **DEVICE AND METHOD FOR INTRACAVITARY CANCER TREATMENT**

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[21] Appl. No.: **09/036,942**

[22] Filed: **Mar. 9, 1998**

[51] **Int. Cl.**[7] **A61N 5/00**

[52] **U.S. Cl.** **600/3**

[58] **Field of Search** 600/1–8

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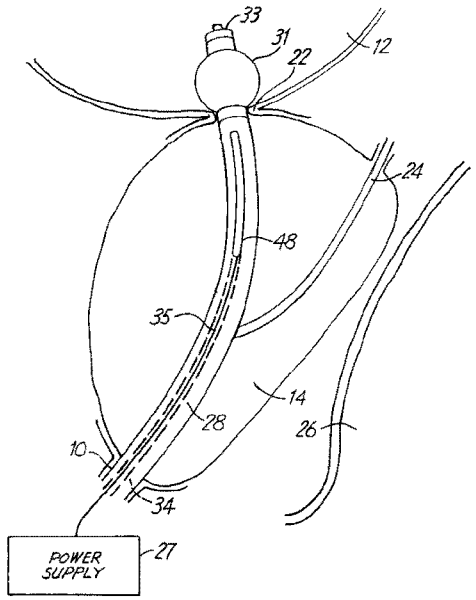
[57] **ABSTRACT**

A device and method for treatment of cancerous tissue from a body conduit involves insertion into the body conduit of a probe including an energy-emitting element for delivering ionizing energy. The body conduit is dilated to decrease a distance between at least a portion of the body conduit and the cancerous tissue. Ionizing energy is delivered from the energy-emitting element to selectively injure the cancerous tissue, with dilation of the body conduit minimizing the radiation dose delivered to the body conduit for a given radiation dose delivered to the cancerous tissue.

32 Claims, 9 Drawing Sheets



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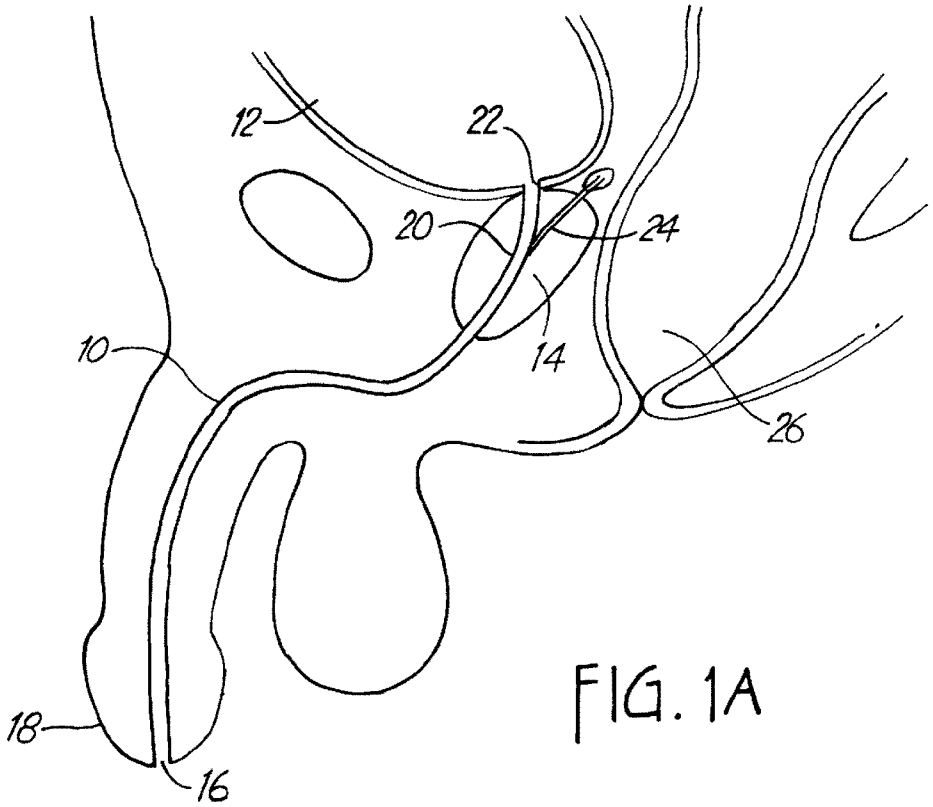

FIG. 1A

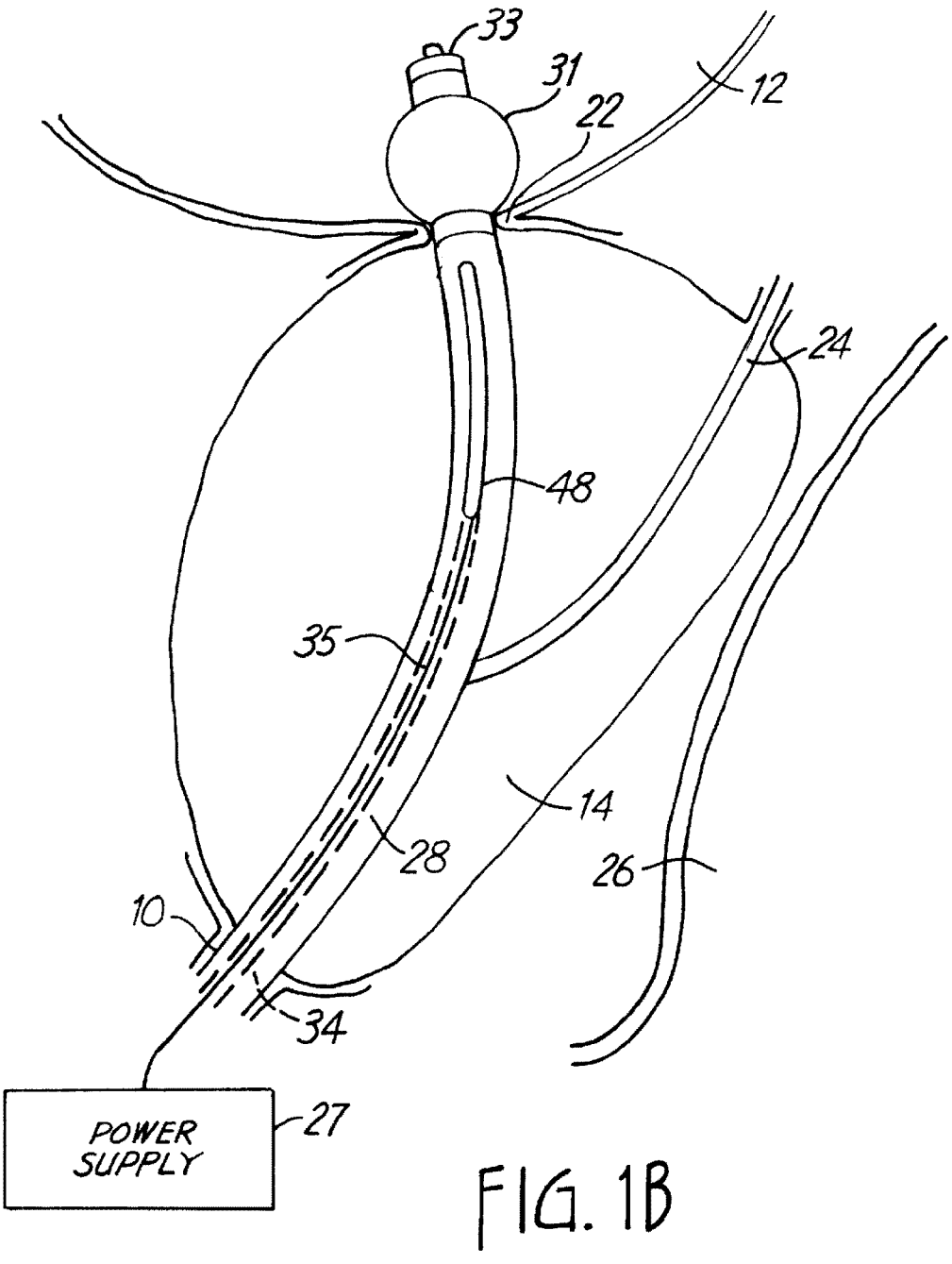

FIG. 1B

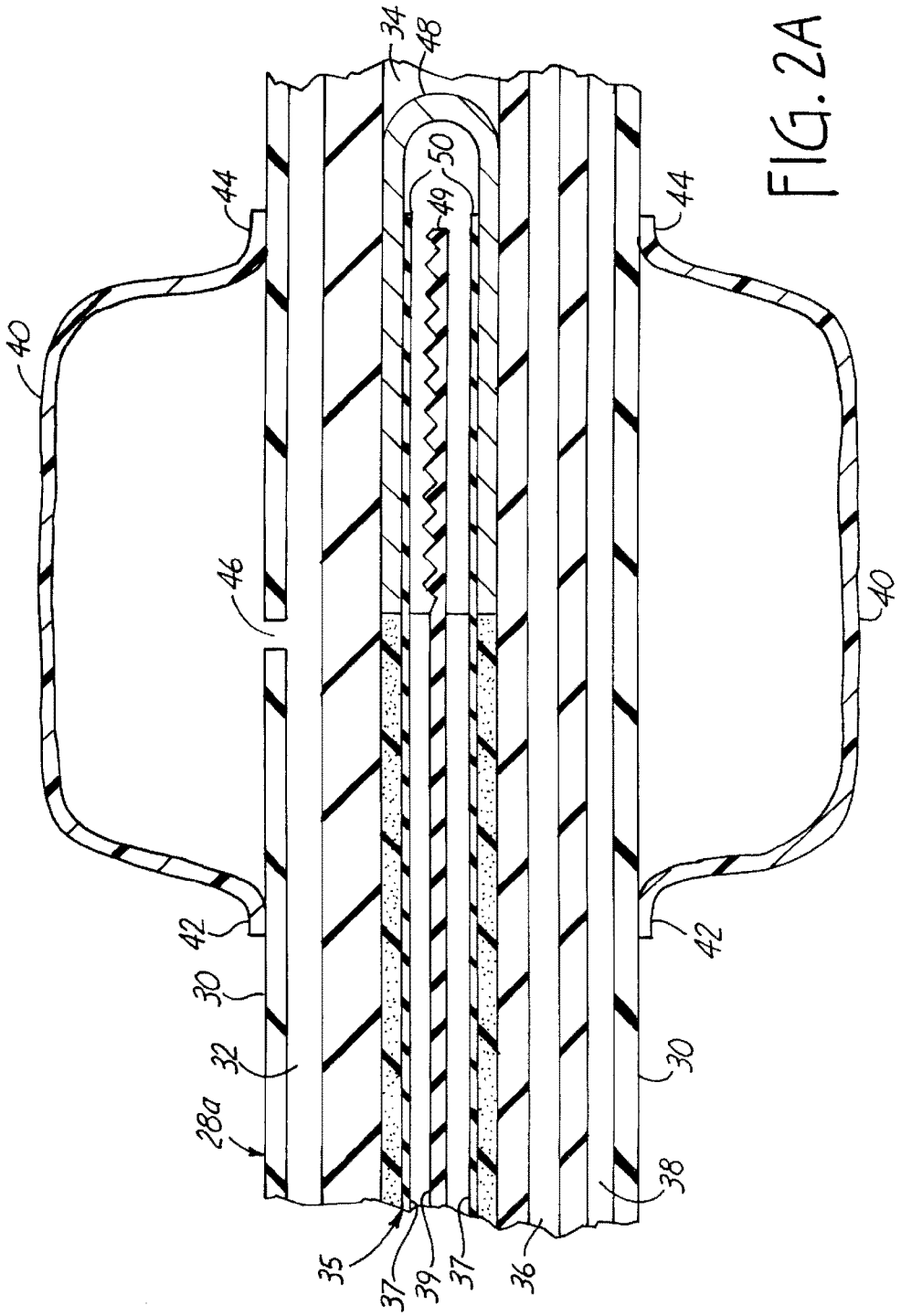

FIG. 2A

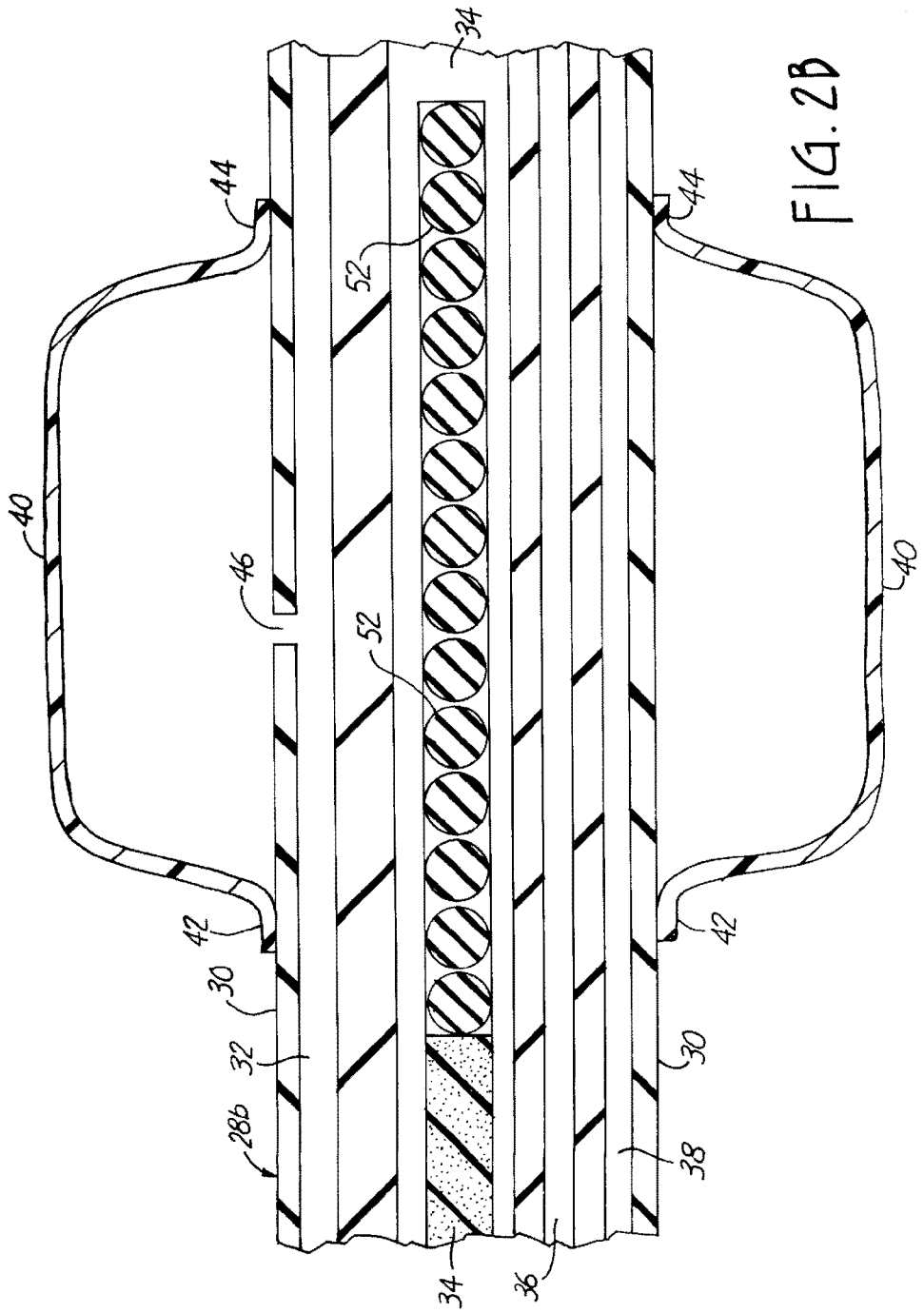

FIG. 2B

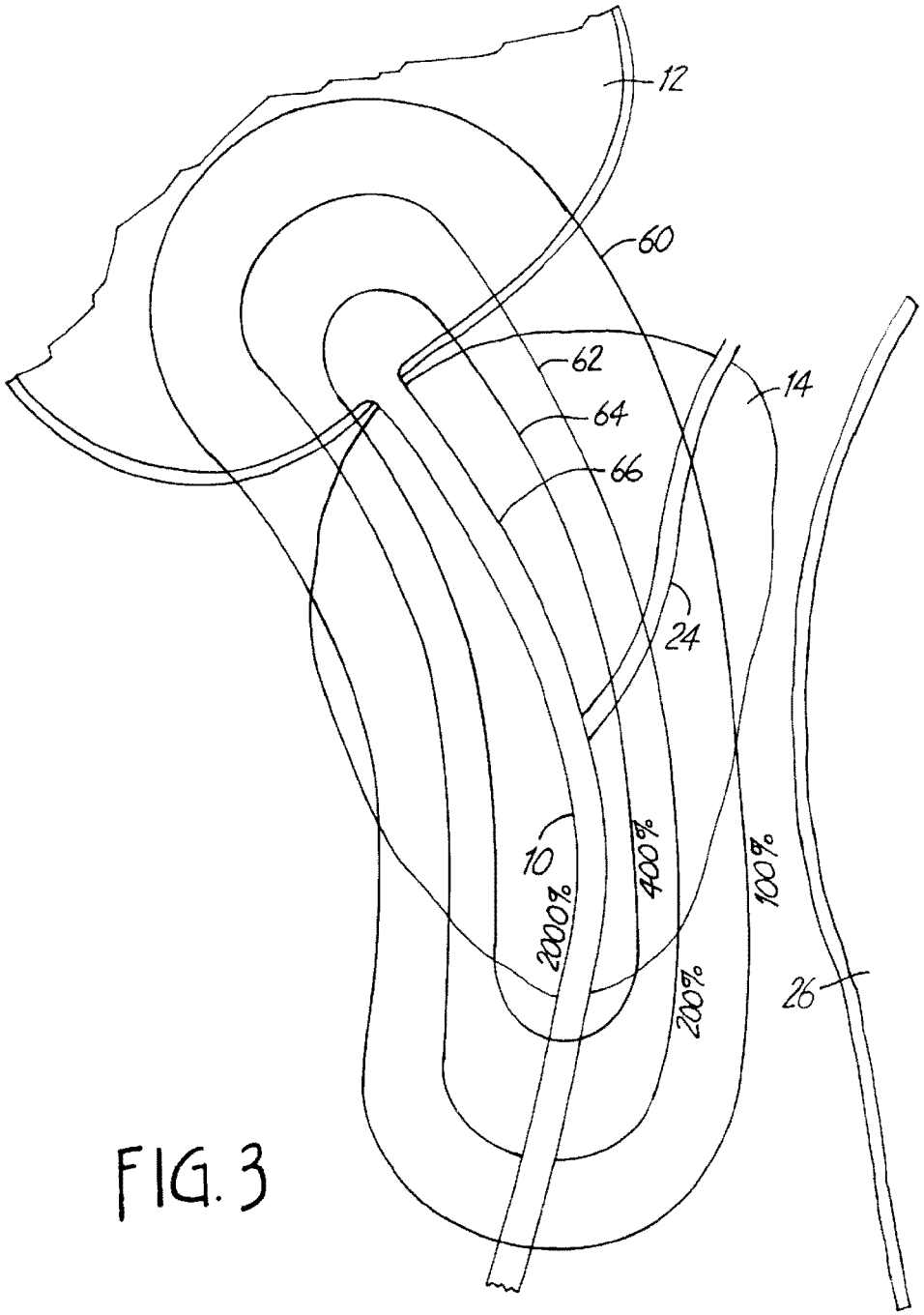

FIG. 3

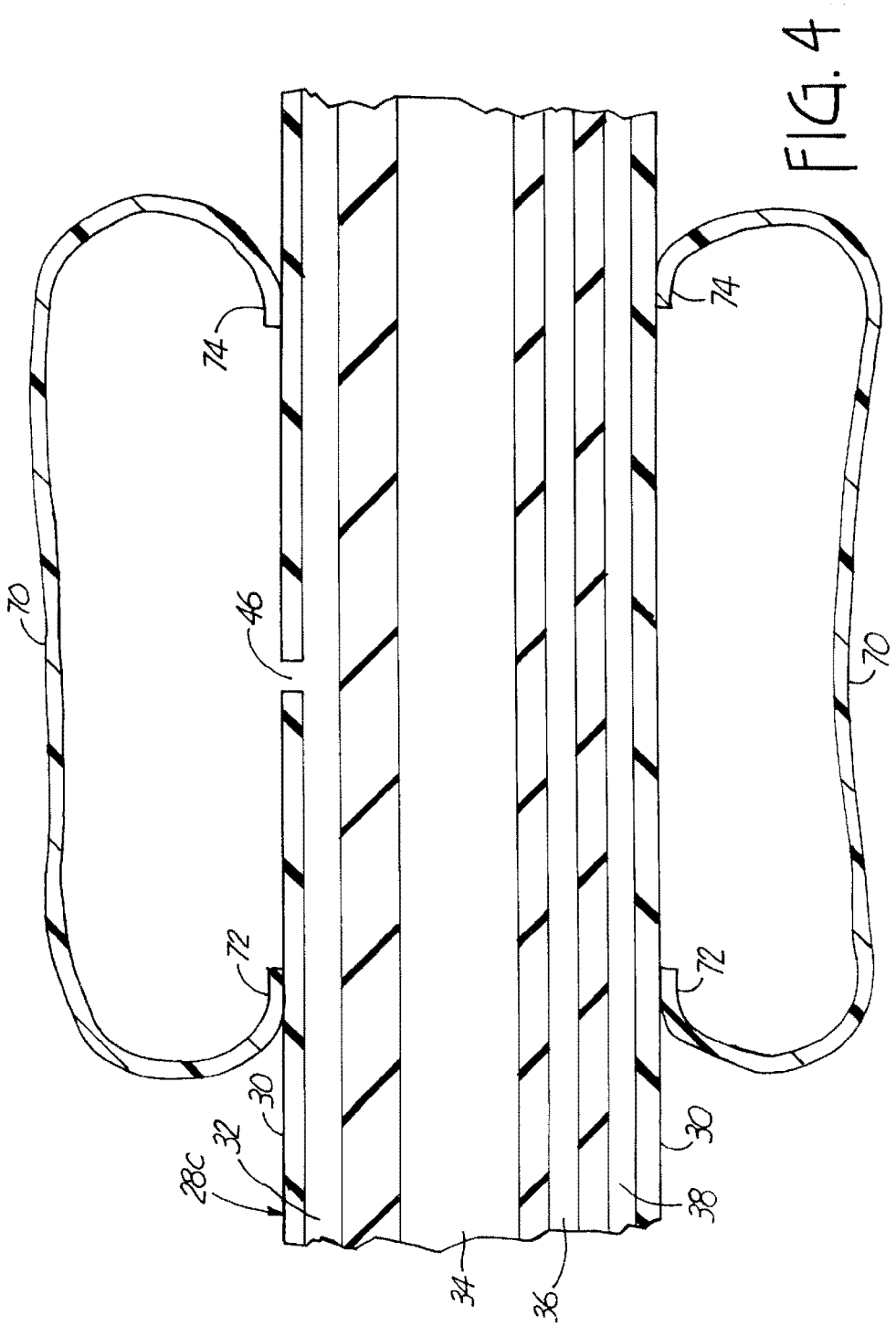

FIG. 4

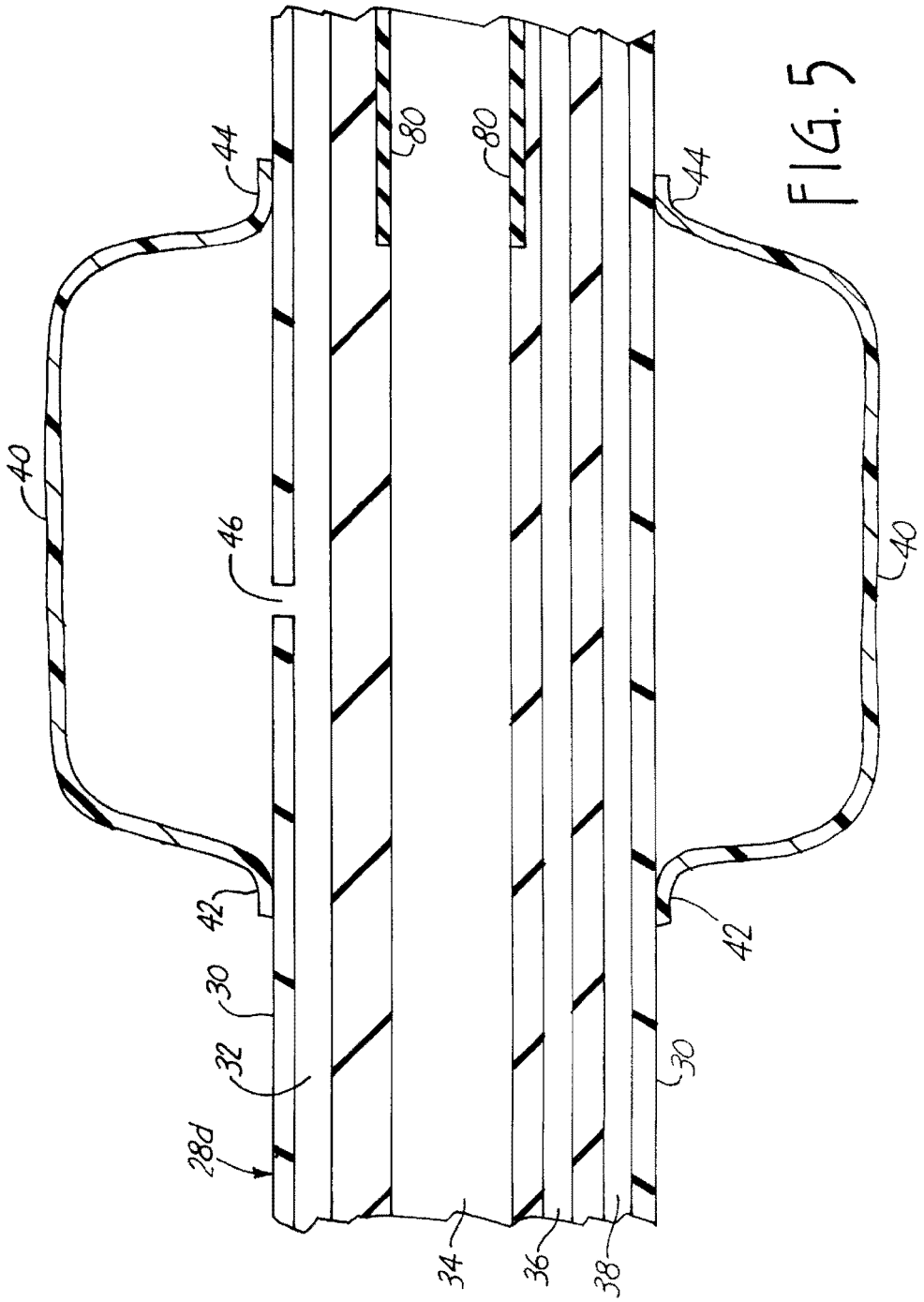

FIG. 5

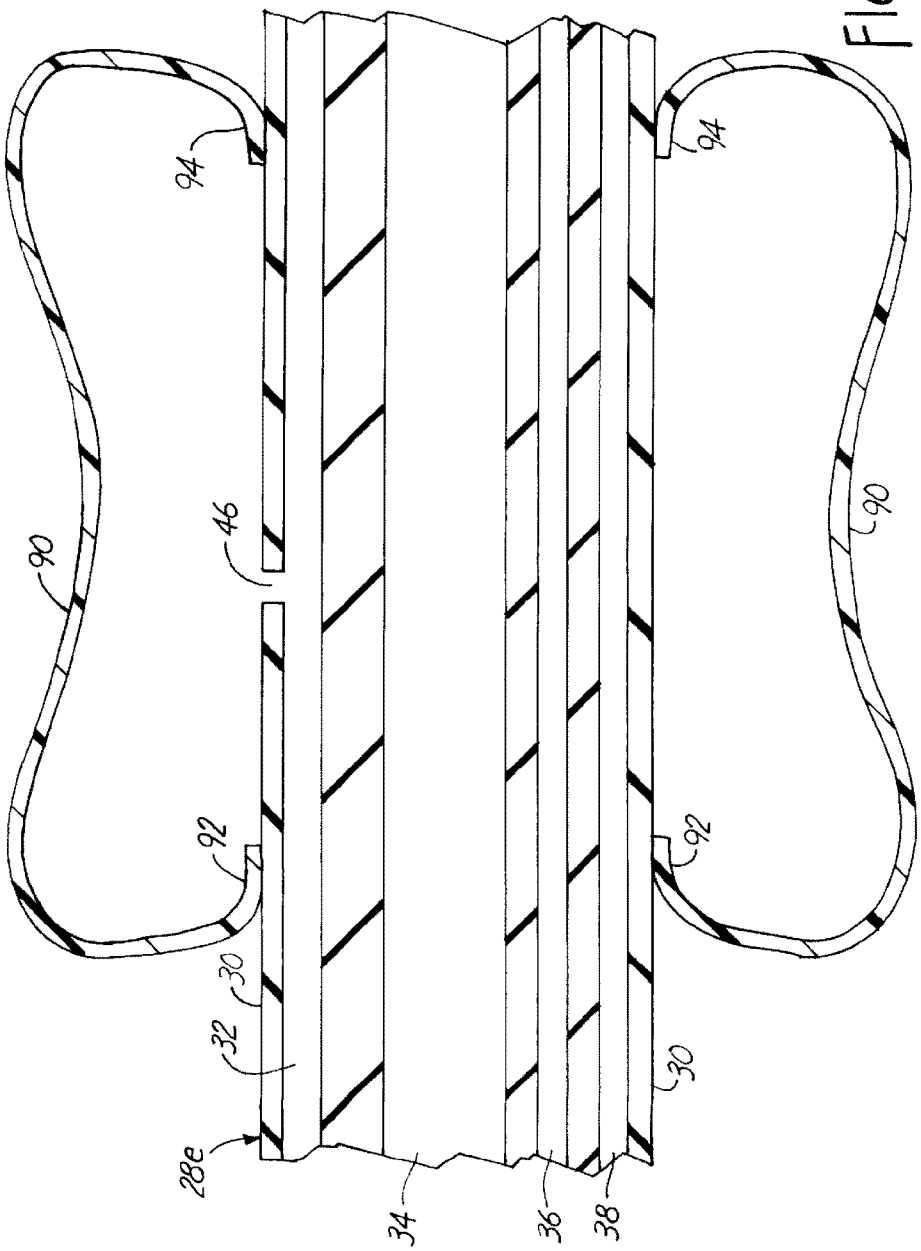

FIG. 6

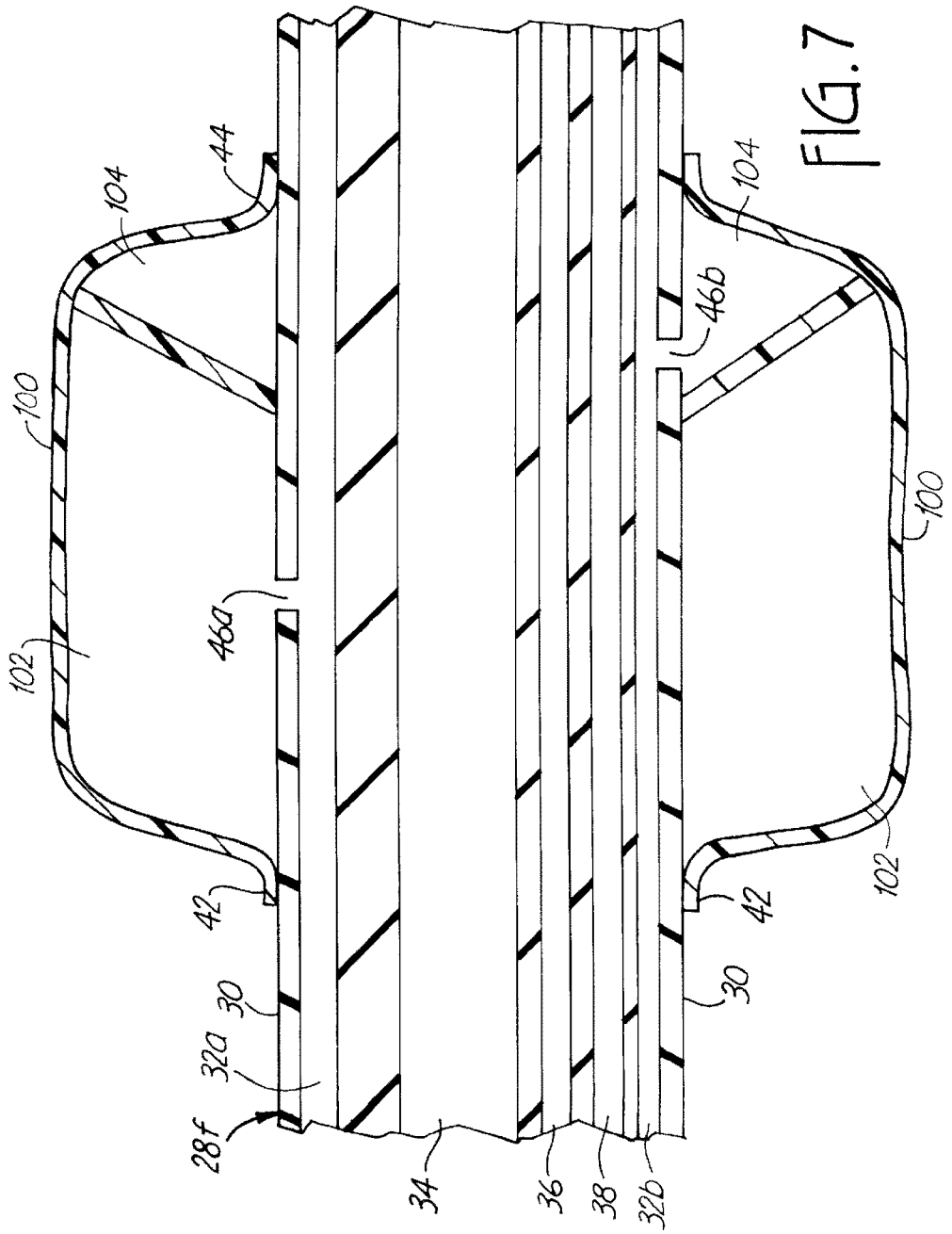

FIG. 7

DEVICE AND METHOD FOR INTRACAVITARY CANCER TREATMENT

BACKGROUND OF THE INVENTION

The present invention relates to treatment of cancer, and more particularly to an apparatus and method for delivering ionizing energy to a cancerous volume of tissue from a body conduit while minimizing adverse effects on intervening healthy tissue.

Ionizing radiation treatment of cancer has a therapeutic goal of effectively treating the disease without causing intolerable injury in the process. In the context of treating cancerous body tissues by tissue destruction, such as by delivery of ionizing radiation, a more specific statement of the goal is to destroy a targeted volume of cancerous tissue without destroying healthy tissue. Where ionizing radiation is used, it is important to deliver a sufficient radiation dose to effectively destroy the targeted cancerous tissue while limiting the dose delivered to healthy tissue to a tolerable level.

Ionizing radiation is useful for treating cancer because at certain doses it has a somewhat selective injurious effect on cancerous cells as compared to healthy cells. Cancerous cells have a shorter reproductive life cycle time than normal cells, by definition. Cells are more vulnerable to damage from radiation at certain phases of the reproductive life cycle than others. For a predetermined number of cells, at any given time, more cancerous cells than normal cells are in a vulnerable phase and are therefore vulnerable to radiation damage. Consequently, in the same amount of time, more cancerous cells are injured than healthy cells by the same dose of radiation. Due to the more frequent occurrence of reproductive cell cycle phases, cancerous cells have a shorter opportunity to repair damage and therefore are more statistically likely to be irreversibly damaged by radiation than normal cells. Intermittent or fractionated doses of radiation further improve the ability of radiation therapy to destroy a greater proportion of cancerous tissue.

One technique employed to selectively treat cancerous body tissue is known as external beam radiation therapy (EBRT). According to this method, a target volume of cancerous tissue is located and an external ionizing radiation beam is sequentially focused on the target tissue from multiple angles. The intensity of ionizing radiation from a point source is generally inversely proportional to the square of the distance from the source, so that only a relatively small dose of energy may be delivered from a significant distance to the target tissue by the beam without delivering unacceptably high amounts of energy to intervening tissue between the external beam source and the target tissue. However, this effect is mitigated somewhat by employment of multiple beam angles, with the beam angles being selected to overlap only within the target volume, so that the dose delivered to the target tissue is the sum of the doses delivered by each beam while the dose delivered to intervening tissue is only that provided by a single beam. Another method utilized with EBRT involves delivering fractionated radiation doses. This technique, using multiple sublethal doses, allows intervening healthy tissue to repair the damage induced by radiation in the interval between doses, whereas a greater proportion of cancerous cells undergo reproductive cycle phases. The crossed-beam approach enables EBRT to be used with improved therapeutic effect, although the dose deliverable to the target tissue without harming intervening tissue remains less than optimal.

One significant problem with EBRT is the margin necessary to accommodate movement or shifting of the prostatic capsule. The prostate is not bound in a particular position within the pelvic region of the body, allowing the prostatic capsule to shift upon movement of the body. Mapping of the location of cancerous tissue within the prostate is typically performed in a procedure that is separate from the actual EBRT procedure, such that the cancerous tissue in the prostatic capsule may have shifted from its mapped position during the subsequent EBRT session. In order to ensure that a sufficient dose of radiation is delivered to the cancerous tissue, a margin must be provided to accommodate all of the possible positions of the cancerous tissue; that is, the volume within which the beam angles overlap is increased to include this margin. As a result, healthy tissue located within the margin is necessarily exposed to a higher dose of radiation than would otherwise be desired, limiting the dose deliverable to the cancerous tissue without causing intolerable damage to healthy tissue.

Another approach to treatment of cancerous body tissue involves combining EBRT with radioactive seed implantation, or interstitial brachytherapy. This procedure involves implanting encapsulated radioisotopes in or near the cancerous tissue to be treated, thereby delivering the highest dose of energy to tissue immediately adjacent the radiating seeds, in addition to performing crossed-beam EBRT to deliver radiation energy to the target volume. Seed therapy is often referred to by the broad term brachytherapy, meaning therapy delivered by a source located near or within the diseased area to be treated. The use of radioactive seeds allows the EBRT dose to be reduced. Consequently, the total dose to healthy tissue is reduced, resulting in reduced morbidity (i.e., impotence, incontinence, inflammation). In addition, the problems of displacement of cancerous tissue due to shifting of the prostatic capsule are reduced, since the seeds are able to move along with the targeted cancerous tissue. However, the use of radioactive seeds typically requires an invasive, interstitial implantation procedure that increases the complexity of the procedure and presents a risk of residual morbidity and side effects such as infection, incontinence, or impotence.

There is a continuing need for a minimally invasive solution to deliver effective doses of ionizing radiation to cancerous tissue while controlling doses to healthy tissue at tolerable levels.

SUMMARY OF THE INVENTION

The present invention is a device and method for treatment of cancerous tissue from a body conduit. A probe is inserted into the body conduit, and includes an energy-emitting element for delivering ionizing energy. The body conduit is dilated to decrease a distance between at least a portion of the body conduit and the cancerous tissue. Ionizing energy is delivered from the energy-emitting element to injure the cancerous tissue, with dilation of the body conduit decreasing the radiation dose delivered to the body conduit for a given radiation dose delivered to the cancerous tissue.

In one embodiment, selected energies of ionizing radiation delivered from the energy-emitting element are absorbed, and the selected energies of ionizing radiation absorbed may vary along a length of the energy-emitting element. In another embodiment, at least a portion of the energy-emitting element is shielded to produce a radiation pattern that spatially varies along a length of the probe.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A is a vertical sectional view of a male pelvic region showing the relative position of urinary organs near the prostate.

FIG. **1B** is an enlarged view of the male pelvic region of FIG. **1A** showing a urethral catheter positioned within the prostate region.

FIG. **2A** is a sectional view of an energy-delivering portion of a probe according to a first embodiment of the present invention.

FIG. **2B** is a sectional view of an energy-delivering portion of a probe according to a second embodiment of the present invention.

FIG. **3** is a diagram illustrating typical isodose curves for ionizing radiation delivered from the urethra.

FIG. **4** is a sectional view of an energy delivering portion of a probe according to a third embodiment of the present invention.

FIG. **5** is a sectional view of an energy-delivering portion of a probe according to a fourth embodiment of the present invention.

FIG. **6** is a sectional view of an energy-delivering portion of a probe according to a fifth embodiment of the present invention.

FIG. **7** is a sectional view of an energy-delivering portion of a probe according to a sixth embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Throughout this detailed description, the present invention will be described as it pertains to transurethral brachytherapy for treatment of prostate cancer. It will be understood by those skilled in the art that certain principles of the present invention may also be applied to treatment of other cancers from nearby body conduits.

FIG. **1A** is a vertical sectional view of a male pelvic region showing the relative position of urinary organs near the prostate **14**. Urethra **10** is a duct leading from bladder **12**, through prostate **14** and out orifice **16** of penis end **18**. Urethra **10** includes a prostatic portion **20** passing through prostate **14**. When prostate **14** is afflicted with cancer, tissue around the periphery of the prostatic capsule is typically among the tissue that is determined to contain cancer. In order to treat the cancerous tissue around the periphery of prostate **14**, it is necessary to deliver energy (such as ionizing radiation) to the cancerous tissue with sufficient intensity and for a sufficient time to injure the cancerous tissue. It is also important to avoid intolerable damage to urethra **10** and to adjacent healthy tissues, such as intervening tissue in prostate **14**, ejaculatory duct **24** and rectum **26**. Selective damage to the cancerous tissue within prostate **14** is made possible by an ionizing energy-delivering probe according to the present invention, which is shown in FIGS. **2A**, **2B** and **4–7**.

FIG. **1B** shows an enlarged view of the male pelvic region of FIG. **1A** with probe **28** properly positioned within urethra **10**. Probe **28** includes a central energy delivery lumen **34** for housing a radiation-emitting source, such as x-ray tube **48** (shown schematically) in one embodiment, with cable **35** provided to couple x-ray tube **48** to power supply **27** in a manner known in the art. In one embodiment, x-ray tube **48** is axially movable along the length of probe **28** to enable treatment of cancerous tissue located anywhere within prostate **14**. In another embodiment, a radiation source may be employed that has an active length extending along the entire length of prostate **14**, such that axial movement of the radiation source is unnecessary. Cable **35** is preferably a state of the art high voltage coaxial cable exhibiting substantial high voltage holdoff, such as is known in the art for safely delivering high voltage power signals and is commercially available from manufacturers such as New England Wire & Cable, for example. As is known in the art, retention balloon **31** at distal end **33** of probe **28** is inflatable in bladder **12** to secure probe **28** at a predetermined axial location of urethra **10**.

FIG. **2A** is a sectional view of an energy-delivering portion of probe **28***a* according to the present invention, with the radial dimension greatly exaggerated for the sake of clarity. Probe **28***a* is preferably a Foley-type urethral catheter made of a flexible, medical-grade elastomer, as is known in the art. Probe **28***a* generally has an outer diameter between about 16 and 22 French, and includes outer surface **30** which is generally circular in cross-section. The overall length of probe **28***a* allows a distal end thereof to be inserted through urethra **10** and into bladder **12**; however, FIG. **2A** shows only an energy-delivering portion of probe **28***a*. In one preferred embodiment, probe **28***a* is coated with a hydrophilic solution, such as is sold by Hydromer, Inc. under the mark Hydromer, which lubricates outer surface **30** of probe **28***a* and facilitates its advancement within urethra **10**.

Probe **28***a* is a multi-lumen shaft including dilatation balloon inflation lumen **32**, energy delivery lumen **34**, urine drainage lumen **36**, and retention balloon inflation lumen **38**. In some embodiments, probe **28***a* may further include a cooling system (not shown) for circulation of a cooling fluid to cool the radiation source within energy delivery lumen **34**, as well as other lumens for various purposes, as generally described in U.S. Pat. No. 5,300,099 assigned to Urologix, Inc., which is hereby incorporated by reference. Probe **28***a* also includes dilatation balloon **40** sealingly attached to outer surface **30** and in fluid communication with dilatation balloon inflation lumen **32**.

Urine drainage lumen **36** is adapted to facilitate the flow of urine from bladder **12** through probe **28***a*, in a manner known in the art. Retention balloon inflation lumen **38** is adapted to communicate an inflation fluid to a Foley-type retention balloon **31** (FIG. **1B**) at distal end **33** of probe **28***a* in bladder **12** to locate probe **28***a* within the urethra, as is known in the art. Urine drainage lumen **36** is generally required only when the duration of treatment is such that the patient will experience discomfort from accumulation of urine within bladder **12** during the treatment session.

Dilatation balloon **40** is secured over probe **28***a* by bonding balloon waists **42** and **44** over outer surface **30**. Dilatation balloon **40** is inflated by supplying pressurized fluid through dilatation balloon inflation lumen **32**, which communicates with the interior of dilatation balloon **40** through aperture **46** in outer surface **30** of probe **28***a*. In an exemplary embodiment, dilatation balloon **40** may be inflated with fluid to a radius extending 0.5 cm beyond outer surface **30** of probe **28***a*, increasing the typical total distance from the center of probe **28***a* to the outer surface of dilatation balloon (and thus the wall of urethra **10**) from 0.3 cm to 0.8 cm. Balloon **40** may be provided with a larger or smaller radius as necessary for proper treatment. It will be appreciated by one skilled in the art that balloon **40** is a well-known example of a dilatation mechanism, and that other configurations may be used to similarly dilate urethra **10**.

In the embodiment shown in FIG. **2A**, energy delivery lumen **34** contains a miniature radiation-emitting tube **48** for emitting ionizing radiation radially outwardly from probe **28***a*. Tube **48** is preferably positioned adjacent dilatation balloon **40**, and may for example be movable along the axial length of probe **28***a* within energy delivery lumen **34**.

Radiation-emitting tube **48** is constructed in a manner known in the art, and may for example comprise an evacuated glass tube containing cathode **49** and anode **50**. Cathode **49** may for example be connected to inner conductor **39** of coaxial high-voltage cable **35**, and anode **50** may for example be connected to outer conductor **37** of cable **35**. In an exemplary embodiment, cathode **49** may be a tungsten filament heated to a temperature sufficiently high to cause electrons to reach velocities that allow them to escape from the filament. Anode **50** typically has a very high positive potential, and is positioned around the inside perimeter of tube **48** in an exemplary embodiment, and may also be formed of tungsten. The escaping electrons are attracted to anode **50**, and are accelerated to a high velocity before colliding with anode **50** and consequently ejecting inner-shell electrons from the tungsten anode atoms. X-rays and other emissions are created when the high-energy electrons return to normal positions in the tungsten atoms' electron shells. The energy gained by the participating electrons is measured in electron-volts (eV). Tube **48** is preferably operable to produce x-ray radiation photons having energies in the 15 keV to 50 keV range to achieve proper depth penetration (2–3 cm, for example) with the desired dose for treatment of cancerous tissue in prostate **14**. It will be understood by one skilled in the art that numerous other cathode and anode configurations and arrangements of high-voltage sourcing cable **35** may be used to achieve the preferred radiation-emitting characteristics of the present invention.

FIG. **2**B is a sectional view of an energy-delivering portion of probe **50** according to an alternate embodiment of the present invention. Probe **28***b* shown in FIG. **2**B is identical to probe **28***a* shown in FIG. **2**A, except that energy delivery lumen **34** contains a plurality of radiation-emitting seeds **52** rather than a radiation-emitting tube. FIG. **2**B illustrates a plurality of seeds **52** essentially forming a linear source; in an alternative embodiment, a lesser number of seeds may be employed and implemented in such a manner that the seeds are movable along the axial length of probe **28***b* within energy delivery lumen **34**. Seeds **52** are composed of a radiation-emitting material as is known in the art, such as iodine-125, palladium-103 or thallium-201 in exemplary embodiments, typically encased in titanium, for example. Seeds **52** are chosen to operate to produce radiation photons having energies greater than about 15 keV to achieve proper depth penetration (2–3 cm, for example) with the desired dose for treatment of cancerous tissue in prostate 14. In a further alternative embodiment, dilatation balloon **40** may itself be filled with a treatment fluid for emitting ionizing radiation, eliminating the need for energy delivery lumen **34** and a radiation source enclosed therein.

In order to better understand the relationship between radiation intensity and depth of penetration, a brief discussion of the phenomena that occur in tissue upon exposure to x-ray radiation is beneficial. These phenomena are known as Elastic Scattering, Photoelectric Absorption, Compton Scattering, and Electron Pair Production. Elastic Scattering has no substantive effect on x-ray radiation therapy, and Electron Pair Production occurs only at energy levels significantly higher than the 15–50 keV range utilized by the present invention, leaving only Photoelectric Absorption and Compton Scattering of interest.

Photoelectric Absorption is a process where a photon interacts with an electron in one of the inner shells of an atom of the absorbing tissue material, and has a greater probability of occuring when the energy of the photon is equal to the energy binding the innermost electrons in the absorbing tissue material atom. The photon is absorbed by the subject electron, and therefore gives up all of its energy to the subject electron, some of which is used to overcome the binding energy of the electron and release it from its orbit, and the remainder of which is imparted to the electron in the form of kinetic energy of motion. The vacancy left in the atomic shell due to the ejection of the electron must be filled by another electron falling in from an outer shell of the atom or by a conduction electron from outside the atom, causing emission of a low energy photon to balance the decrease in potential energy of the incoming electron.

Compton Scattering is a process where a photon interacts with a "orbital" electron, an electron whose binding energy is negligibly small compared with the energy of the photon. Only a portion of the photon's energy is given to the electron as kinetic energy, and the photon is deflected at an angle and continues on its way with whatever energy remains. The reaction transforms the incident photon into a fast electron and a photon of reduced energy, which may go on to take part in further interactions (either by Photoelectric Absorption or by Compton Scattering, depending on the remaining energy of the photon). In any given case the incident photon may lose very little to a large fraction of its energy. In practice, when an x-ray beam is absorbed by tissue, a vast number of photons interact with a vast number of atoms, and on a statistical basis all possible energy losses will occur. The net result is the production of a large number of fast electrons, many of which can ionize other atoms and initiate the change of events that ultimately is expressed as biological damage.

Therefore, higher energy radiation is able to achieve deeper penetration in tissue than lower energy radiation, due to the higher energy photon's ability to continue on with reduced energy after an interaction. The radiation dose decreases at increasing distances from the radiation source, due to the complete absorption of the some of the x-ray photons as the radiation travels through the tissue. For a more complete discussion of the phenomena of radiation absorption, see chapter one of *Radiation for the Radiologist* by Eric J. Hall.

FIG. **3** is a diagram illustrating typical isodose curves (that is, curves upon which the dose of ionizing energy delivered to tissue is equal) for ionizing radiation delivered from a source centered within urethra **10** (such as within energy delivery lumen **34** of probes **28***a* and **28***b*, FIGS. **2**A and **2**B). The isodose curves are based on the assumption that a selected target volume of tissue within prostate **14** has been located, and the radiation source within urethra **10** is operated so that the 100% isodose curve **60** runs through the target volume of prostate tissue. Since cancerous prostate tissue is often located near the periphery of prostate **14**, FIG. **3** illustrates the 100% isodose curve **60** near the periphery of prostate **14**.

For the exemplary case shown in FIG. **3**, isodose curve **60** is approximately 2.0 cm from the center of urethra **10**. 200% isodose curve **62** is approximately 1.0 cm from the center of urethra **10**. 400% isodose curve **64** is approximately 0.5 cm from the center of urethra **10**. The wall of urethra **10**, when urethra **10** is not dilated, is approximately 0.1 cm from the center of urethra **10** in one exemplary embodiment (where a probe carrying a radiation-emitting source has a radius of 0.1 cm), which is about on the 2000 % isodose curve. The unit Gray (Gy), equal to an energy absorption of 1 joule/kg or 100 rads, is a standard unit of absorbed radiation intensity. Thus, for a desired therapeutic ionizing radiation intensity of 15 Gy (which is within the range suitable as a "boost dose" for use with external beam radiation therapy, for example),

the intensity at 200% isodose curve **62** is 30 Gy, the intensity at 400% isodose curve **64** is 60 Gy, and the intensity at the 2000% isodose curve at the wall of urethra **10** is about 300 Gy. For a desired therapeutic ionizing radiation intensity of 100 Gy (which is within a potential range for singular therapy, without requiring any other radiation therapy), the intensity at 200% isodose curve **62** is 200 Gy, the intensity at 400% isodose curve **64** is 400 Gy, and the intensity at the 2000% isodose curve at the wall of urethra **10** is about 2000 Gy.

For the case of the "boost dose" of 15 Gy delivered to the target prostate tissue, the 300 Gy of radiation delivered to the urethral wall could potentially harm the healthy tissue of urethra **10**, and could result in some morbidity for the patient. For the case of the therapeutic dose of 100 Gy delivered to the target prostate tissue, the 2000 Gy of radiation delivered to the urethral wall is extremely likely to injure the healthy tissue of urethra **10**.

In order to reduce the damage to healthy tissue between the x-ray source and the target prostate tissue, particularly to urethra **10**, the present invention operates to dilate urethra **10** while delivering the ionizing energy, thereby decreasing the distance between the urethra and the target prostate tissue. As a result, with 100% isodose curve **60** still defined by the location of the target tissue (2.0 cm from the center of urethra **10**), the wall of urethra **10** is essentially displaced outward toward 100% isodose curve **60**. An increase in urethral radius from 0.1 cm (the undilated radius) to 0.5 cm (the dilated radius), for example, moves urethra **10** from the 2000% isodose curve to 400% isodose curve **64**, reducing the intensity of radiation at urethra **10** by a factor of five. For the "boost dose" example, where the 100% intensity dose is 15 Gy, the radiation intensity at urethra **10** drops from 300 Gy (undilated) to 60 Gy (dilated). For the therapeutic dose example, where the 100% intensity dose is 100 Gy, the radiation intensity at urethra **10** drops from 2000 Gy to 400 Gy. Additional dilatation of urethra **10** decreases the intensity of radiation at urethra **10** even further, potentially to a tolerable dose that will not permanently harm urethra **10**, particularly in combination with fractionation of the dose delivered. The present invention therefore provides a solution for delivering ionizing radiation to cancerous prostate tissue from a minimally invasive urethral probe while decreasing the damage to intervening healthy tissue such as the wall of urethra **10**.

Prostate **14** (see, e.g., FIG. 1A) is not entirely stationary within the pelvic region of the body. Movement of the body, or even dilatation of urethra **10**, could potentially cause displacement of the prostatic capsule. The present invention is still effective when dilatation of urethra **10** causes prostate **14** to be displaced further away from urethra **10**, because of the geometric properties of the displacement and of radiation therapy.

Geometrically, an increase in the radius of urethra **10** increases the radius of prostate **14** as well, but by a lesser amount. For the sake of clarity, urethra **10** may be modeled as a cylinder of radius R_1 and prostate **14** may be modeled as a sphere of radius R_2. Consider an example of a probe that has a radius of 0.3 cm and contains a radiation-emitting source, such that urethral radius R_1 is 0.3 cm, and a prostate having a prostatic radius R_2 of 2.25 cm. The prostatic portion of the urethral cylinder therefore has a length (l) of 4.5 cm (equal to the diameter of the prostatic sphere). The volume (V_1) of the urethral cylinder is expressed as:

$$V_1=\pi R_1^2 l$$

and the volume of the prostatic sphere (V_2) is expressed as:

$$V_2 = \frac{4}{3}\pi R_2^3$$

Thus, V_1 is 1.27 cm^3 for the model parameters given above. When R_1 is increased by dilatation of urethra **10** from 0.3 cm to 0.8 cm, for example, V_1 increases to 9.04 cm^3. Thus, the volume of prostate tissue that is displaced by dilatation of urethra **10** is the difference between the two urethral volumes, or 7.77 cm^3. This displaced volume of tissue essentially appears as an expansion of the outer perimeter of the prostatic sphere. The volume of the prostatic sphere when urethra **10** is not dilated is 47.7 cm^3 for the model parameters given above. By adding the volume of tissue displaced by dilatation of urethra **10** (7.77 cm^3) to the volume of the prostatic sphere when urethra **10** is not dilated (47.7 cm^3), the total volume of the prostatic sphere when urethra **10** is dilated is determined as 55.47 cm^3. Inserting this number into the equation for the volume of the prostatic sphere given above and solving for the radius yields a value of 2.36 cm for R_2. Thus, an increase in the radius of urethra **10** from 0.3 cm to 0.8 cm (0.5 cm increase) results in an increase in radius of prostate **14** from 2.25 cm to 2.36 cm (0.11 cm increase). The increase in the radius of prostate **14** is therefore significantly less than the increase in the radius of urethra **10** due to dilatation. Thus, only a small increase in the radiation energy delivered from a probe within urethra **10** is required to reach the perimeter of prostate **14** at the target dose level. Even though the radiation energy delivered from the probe is slightly increased, the increased spatial separation between the radiation-emitting source within urethra **10** and the dilated wall of urethra **10** results in a significant net decrease in the radiation intensity delivered to the wall of urethra **10**.

The geometric effect explained above is further enhanced by the nature of radiation dosimetry, where an increase in radius has a greater dose reduction effect close to the source than distant from the source. The radiation-emitting source is modeled as a linear source (which may be implemented by an actual linear source such as a row of seeds or a ribbon, or by a point source swept along the axial length of tissue to be treated), in which case the intensity of radiation delivered to tissue is generally proportional to the inverse of the radial distance from the source. In the example given above, the urethra is dilated from 0.3 cm to 0.8 cm in radius, and the peripheral prostate tissue is displaced from a radius of 2.25 cm to 2.36 cm. In order to provide an effective radiation dose to the periphery of prostate **14**, the energy of the radiation-emitting source must be increased to shift the 100% isodose curve outward from 2.25 cm to 2.36 cm. For a therapeutic dose example, where the radiation dose at the 100% isodose curve is 100 Gy, Table 1 shown below summarizes the doses delivered at various distances from the center of urethra **10** for both the undilated case (urethral wall at 0.3 cm, prostatic capsule at 2.25 cm) and the dilated case (urethral wall at 0.8 cm, prostatic capsule at 2.36 cm):

TABLE 1

	0.3 cm	0.8 cm	1.0 cm	2.0 cm	2.25 cm	2.36 cm
Undilated	750 Gy (750%)	281.3 Gy (281.3%)	225 Gy (225%)	112.5 Gy (112.5%)	100 Gy (100%)	95.3 Gy (95.3%)
Dilated	786.7 Gy (786.7%)	295 Gy (295%)	236 Gy (236%)	118 Gy (118%)	104.9 Gy (104.9%)	100 Gy (100%)

As shown in Table 1, dilatation of the urethra from 0.3 cm to 0.8 cm reduces the radiation dose delivered to the urethra from 750 Gy to 295 Gy (over a factor of 2.5), a significantly more tolerable level of radiation. Greater or lesser dilatation of urethra **10** may be effected according to the radiation dose delivered to urethra **10** required to prevent intolerable damage to urethra **10** and the characteristics of morbidity associated therewith for a given radiation dose delivered to cancerous tissue.

In an alternative embodiment of the invention, prostate **14** may be prevented from moving by employing certain methods to stabilize the prostatic capsule. For example, bladder **12** may be filled with fluid to prevent the prostatic capsule from being dilated toward bladder **12**. A spatula or other hard instrument may be inserted in rectum **26** to prevent the prostatic capsule from being displaced toward rectum **26**. These procedures effectively obviate the need to increase the intensity of the radiation source within urethra **10** for outward displacement of target tissue in prostate **14**, thereby also reducing the radiation dose delivered to urethra **10** at any particular radius. Dilatation according to the present invention further reduces the radiation dose delivered to urethra **10** by increasing the distance from the radiation source to the urethra for the predetermined target tissue location.

Probe **28***a* for implementing the present invention, shown in FIG. **2**A, illustrates a conventionally shaped dilatation balloon **40**, which is inflatable to dilate urethra **10** during delivery of ionizing radiation and thereby minimize damage to urethral tissue. FIG. **4** shows an energy-delivering portion of an alternate probe **28***c* (with the radiation source within energy delivery lumen **34** omitted for the sake of clarity) utilizing an inflatable dilatation balloon **70** having a shape when inflated that approximates the shape of the 400% isodose curve (see FIG. **3**). By approximating the shape of the isodose curve, balloon **70** is able to ensure that all points of urethra **10** receive the same dose of ionizing radiation, so that the entire urethra **10** is affected in the same way by the radiation therapy treatment.

In order to further minimize the damage done to urethra **10** during radiation therapy, dilatation balloon **40** (FIGS. **2**A and **2**B) or dilatation balloon **70** (FIG. **4**) may be inflated with a fluid containing metallic particles. The metals for commixing with the fluid used to inflate the dilatation balloon are selected to absorb radiation having energies at the low end of the therapeutic radiation range, thereby reducing the effects of the radiation near the energy source (which ordinarily is substantially affected by the low energy radiation) while having a lesser impact on the effects of the radiation distant from the energy source (which ordinarily is affected very little by the low energy radiation). The atomic number of the metal particles substantially determines the efficiency of radiation that they absorb, and the choice of metals to achieve the goal of absorbing certain radiation energies is within the expertise of one skilled in the art. The overall effect of introducing the metal particles into the dilatation balloon inflation fluid is to reduce the radiation dose delivered to the wall of urethra **10**.

As shown in FIG. **3**, delivering ionizing radiation to target tissue in prostate **14** from an unshielded radiation source in urethra **10** exposes tissue around the neck of bladder **12** (at the junction of urethra **10** and bladder **12**) to radiation, which could potentially lead to undesirable side effects such as incontinence. FIG. **5** is a sectional view of a probe **28***d* (with the radiation source within energy delivery lumen **34** omitted for the sake of clarity) that is similar to probes **28***a* (FIG. **2**A), **28***b* (FIG. **2**B) and **28***c* (FIG. **4**) except for the addition of tubular metal shield **80** around energy delivery lumen **34**. Metal shield **80** is composed of a material that absorbs ionizing radiation of particular energy levels, so that a radiation dose profile may be controlled and shaped to protect tissue adjacent the bladder neck and lower sphincter, for example, to avoid potential undesirable side effects resulting from exposure of those regions to radiation. In the embodiment shown in FIG. **5**, shielding **80** is provided around the portion of energy delivery lumen **34** that is located adjacent the bladder neck when probe **28***d* is inserted into urethra **10**, thereby reducing the radiation dose delivered in the bladder neck region. In other embodiments, multiple shields such as metal shields **80** may be provided along the length of a source within energy delivery lumen **34**, composed of different metals and/or different thicknesses of metals along the length of the source to produce more complex radiation dose profiles, as desired for a particular treatment goal. A tubular outer sleeve, for example, may be provided over outer surface **30** of probe **28***d* (with appropriate cut-out sections to accommodate the dilatation balloon) to provide the shielding effect. The sleeve may be composed of different metals or and/or thicknesses of metals along its length, or multiple outer sleeves may be provided, fitting over one another, to vary the shielding effect along the length of probe **28***d*. The sleeve or sleeves may be in a fixed position, or may be movable along the length of probe **28***d*. A sleeve, or multiple sleeves, may alternatively be provided directly over a tube containing the x-ray source within energy delivery lumen **34**, to achieve a similar shielding effect.

FIG. **6** is a sectional view of probe **28***e* (with the radiation source within energy delivery lumen **34** omitted for the sake of clarity) having shaped dilatation balloon **90** for selectively shielding areas of tissue during radiation treatment. Dilatation balloon **90** is attached to outer surface **30** of probe **28***e* at waists **92** and **94**, and is inflated by pressurized fluid flowing through dilatation balloon inflation lumen **32**. The inflation fluid is imbued with metal particles to absorb particular energies of ionizing radiation. The "barbell" shape of dilatation balloon **90** presents a thicker cross-section of fluid at the ends of balloon **90**, thereby providing greater shielding in those regions. Thus, a greater intensity of radiation is delivered through the central portion of dilatation balloon **90**, and a lesser intensity of radiation is delivered to the bladder neck region adjacent the end of balloon **90**, reducing the possibility of undesirable side effects due to radiation exposure of tissue adjacent bladder **12**. Other shapes of balloon **90** may be used to vary the radiation dose pattern along the axial length of probe **28***e* and protect vulnerable anatomical areas from ionizing radiation.

FIG. **7** is a sectional view of probe **28***f* (with the radiation source within energy delivery lumen **34** omitted for the sake of clarity) utilizing dilatation balloon **100** having compartments **102** and **104** therein. Compartment **102** is inflated with pressurized fluid flowing through dilatation balloon inflation lumen **32***a* into compartment **102** through aperture **46***a*. The fluid for inflating compartment **102** is imbued with metal particles to absorb ionizing energy at a first energy

level. Compartment **104** is inflated with pressurized fluid flowing through dilatation balloon inflation lumen **32***b* into compartment **104** through aperture **46***b*. The fluid for inflating compartment **104** is imbued with metal particles to absorb ionizing energy at a second energy level, higher than the first energy level, to provide greater protection from ionizing radiation for tissue adjacent compartment **104**. A plurality of compartments may be provided in balloon **100** with inflation fluids having different metal particles commixed in each compartment, to produce more complex radiation dose patterns. Alternatively, a plurality of separate balloons may be provided along the length of probe **28***f*, each inflated with fluids having different metal particles commixed therein, to produce the desired radiation dose patterns.

In all embodiments of the present invention described above where prostate tissue near the bladder neck does not receive a therapeutic radiation dose due to selective spatial filtering, the tissue may be treated separately by a number of methods. For example, external radiation may be used to target the untreated tissue, radioactive seeds may be placed within the untreated tissue interstitially, or a miniature radiation source may be placed adjacent the lower sphincter. Other methods will be apparent to one skilled in the art. In some cases, it may not even be necessary to separately treat the tissue near the bladder neck, if that tissue is not a part of the targeted cancerous volume of tissue (that is, if the tissue near the bladder neck is not cancerous).

The present invention therefore provides an apparatus and method for treating cancerous tissue from a nearby bodily conduit while minimizing damage to intervening healthy tissue. Various radiation dose patterns may be achieved, to deliver selected amounts of ionizing radiation to different tissue regions. With a radiation-emitting source preferably located at a fixed radius in the bodily conduit, the conduit is dilated to decrease the distance between at least a portion of the bodily conduit and the cancerous tissue, thereby decreasing the radiation dose delivered to the bodily conduit for a given dose delivered to the cancerous tissue.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

We claim:

1. A device for treatment of cancerous prostate tissue from a urethra, comprising:

a probe adapted to be inserted into the urethra, including a retention balloon inflatable in a bladder and an energy-emitting element for delivering ionizing energy to the cancerous prostate tissue; and

a dilator at least partially surrounding the energy-emitting element.

2. The device of claim **1**, wherein the probe includes a balloon inflation lumen and the dilator comprises an inflatable dilatation balloon secured to an outer surface of the probe, the balloon being in fluid communication with the inflation lumen.

3. The device of claim **2**, wherein the dilatation balloon is inflatable to a radius of about 0.5 cm from the outer surface of the probe.

4. The device of claim **2**, wherein the energy-emitting element is capable of delivering ionizing radiation having a first intensity at a first radial distance from the probe corresponding to a periphery of the prostate, and having a second intensity of about four times the first intensity at a second radial distance from the probe corresponding to a periphery of the dilatation balloon when inflated.

5. The device of claim **4**, wherein the first intensity is about 15 Gy and the second intensity is about 60 Gy.

6. The device of claim **2**, wherein the dilatation balloon is inflated with a filtering fluid for absorbing selected energies of the ionizing energy delivered by the energy-emitting element.

7. The device of claim **6**, wherein the filtering fluid is imbued with metal particles selected to absorb the selected energies of ionizing radiation.

8. The device of claim **6**, wherein the dilatation balloon has a shape when inflated with a first thickness at an end of the dilatation balloon and a second thickness less than the first thickness at a center of the dilatation balloon.

9. The device of claim **6**, wherein the dilatation balloon includes a plurality of compartments along a length of the probe.

10. The device of claim **9**, wherein each of the plurality of compartments is inflated with a different filtering fluid to absorb different energies of ionizing radiation along the length of the probe.

11. The device of claim **1**, wherein the energy-emitting element comprises a radiation tube.

12. The device of claim **1**, wherein the energy-emitting element comprises at least one radiating seed.

13. The device of claim **1**, wherein the energy-emitting element is movable along an axial length of the probe.

14. The device of claim **1**, further comprising shielding means around the energy-emitting element for producing a radiation pattern that spatially varies along a length of the probe.

15. The device of claim **14**, wherein the shielding means comprises at least one tubular metal shield around at least a portion of the energy-emitting element.

16. The device of claim **15**, wherein the at least one tubular metal shield is located around an outer surface of the probe.

17. The device of claim **15**, wherein the at least one tubular metal shield is composed of a plurality of metals along its length.

18. The device of claim **14**, wherein the probe includes at least one balloon inflation lumen and the shielding means comprises at least one inflatable dilatation balloon secured to an outer surface of the probe, the at least one dilatation balloon being in fluid communication with the at least one inflation lumen and being inflatable with a filtering fluid for absorbing selected energies of the ionizing energy delivered by the energy-emitting element.

19. The device of claim **18**, wherein the filtering fluid is imbued with metal particles selected to absorb the selected energies of ionizing radiation.

20. The device of claim **18**, wherein the at least one inflatable dilatation balloon comprises a compartmentalized balloon having a plurality of compartments and the at least one inflation lumen comprises a plurality of inflation lumens, respective ones of the inflation lumens being in fluid communication with respective compartments of the compartmentalized balloon.

21. The device of claim **20**, wherein each of the plurality of compartments receives a different filtering fluid to absorb differing energies of ionizing radiation along the length of the probe.

22. The device of claim **18**, wherein the at least one inflatable dilatation balloon comprises a plurality of dilatation balloons and the at least one inflation lumen comprises a plurality of inflation lumens, respective ones of the inflation lumens being in fluid communication with respective ones of the plurality of dilatation balloons.

23. The device of claim 22, wherein each of the plurality of dilatation balloons receives a different filtering fluid to absorb differing energies of ionizing radiation along the length of the probe.

24. A method of treating cancerous prostate tissue comprising:

inserting a probe including an energy-emitting element into a urethra, the probe further including an end portion which extends into a bladder;

securing the end portion of the probe at a base of the bladder;

dilating the urethra; and

delivering a predetermined intensity of ionizing energy from the energy-emitting element for a time sufficient to destroy the cancerous prostate tissue.

25. The method of claim 24, wherein the step of dilating the urethra comprises increasing a radius of the urethra to about 0.5 cm.

26. The method of claim 24, wherein the step of dilating the urethra comprises inflating a balloon secured to an outer surface of the probe.

27. The method of claim 26, wherein the balloon is inflated to a radius of about 0.5 cm from the outer surface of the probe.

28. The method of claim 26, wherein ionizing energy is delivered from the energy-emitting element with a first intensity at a first radial distance from the probe corresponding to a periphery of the prostate, and with a second intensity of about four times the first intensity at a second radial distance from the probe corresponding to a periphery of the balloon when inflated.

29. The method of claim 24, further comprising absorbing selected energies of ionizing radiation delivered from the energy-emitting element.

30. The method of claim 29, wherein the selected energies of ionizing radiation absorbed vary along a length of the energy-emitting element.

31. The method of claim 24, further comprising shielding at least a portion of the energy-emitting element to produce a radiation pattern that spatially varies along a length of the probe.

32. The method of claim 24, wherein the step of securing the end portion of the probe at the base of the bladder comprises inflating a retention balloon at the end portion of the probe.

* * * * *

Exhibit 12

#16/A
3-7,

Docket No.: 101360-16
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Rance A. Winkler, et al.

Application No.: 09/464,727-7988 Group Art Unit: 3736

Filed: December 16, 1999 Examiner: J. Lacyk

For: ASYMMETRIC RADIATION DOSING APPARATUS AND METHOD

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date shown below.

Dated: 2/27/02 Signature: (Ronald E. Cahill)

AMENDMENT

Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Office Action dated October 31, 2001 (Paper No. 5), please amend the above-identified U.S. patent application by replacing all of the claims with the Clean Copy of All Pending Claims below. A Complete Set of Pending Claims With Markings to Show Amendments Made is attached to this Amendment following the signature page.

03/14/2002 SSITHEB1 00000039 99464727
01 FC:215 [illegible]

03/14/2002 SSITHEB1 00000039 99464727
02 FC:202 84.00 OP

Application No.: 09/464,727-7988 Docket No.: 101360-16

Clean Copy of All Pending Claims

1. (Amended) An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves with respect to the apparatus volume.

2. (Amended) A surgical apparatus for providing radiation treatment to target tissue comprising:

A1

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim 2, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim 3, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. (Amended) A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. (Amended) A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim 6, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim 1, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. (Amended) An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

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a radiation source disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume.

10. (Amended) The apparatus of claim 9, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.

11. The apparatus of claim 10, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim 11, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim 9, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim 13, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

15. Canceled.

16. Canceled.

17. Canceled.

18. Canceled.

19. Canceled.

REMARKS/ARGUMENTS

Applicants appreciate the Examiner's indication that claims 2 through 7 define allowable subject matter. Applicants have amended claims 2, 5 and 6 to be independent claims including the recitations of the base claim and any intervening claims and to correct any rejections under 35 U.S.C. § 112, second paragraph. Applicants have also amended the preamble to read that the recited apparatus is a surgical apparatus for providing radiation treatment to target tissue. This amendment is supported in the opening paragraph of the Detailed Description of the Invention.

Applicants have amended independent claim 1 (from which claim 8 depends) and independent claim 9 (from which claims 10 to 14 depend, directly or ultimately) to better define the invention. Applicants have also amended claim 10 to recite that radio-opaque material is disposed ***only*** on a portion of the expandable surface. Applicants cancel claims 15 to 19 herein. Accordingly, claims 1 to 14 are now pending.

Claim Rejections Over McGrath

Claims 1 and 9 stand rejected as anticipated by McGrath (US 6,036,631) under 35 U.S.C. § 102(e). In particular, the Examiner states that "McGrath et al discloses a device for treating tissue having an expandable outer surface and a radiation source disposed within the expandable surface having a plurality of solid radiation sources (Fig. 2B). McGrath et al also teaches the use of shielding to absorb some of the radiation."

McGrath is directed to a device and method for treatment of cancerous tissue from a body conduit, i.e., interluminal treatment. By contrast, Applicants' apparatus is an interstitial brachytherapy apparatus, used to treat remaining proliferative tissue surrounding a surgical extraction site such as might be found in the treatment of brain or breast cancers. As a result of this difference in purpose, there are a number of key differences in structure between McGrath and claims 1 and 9.

For example, the expandable outer surface of claims 1 and 9 defines a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated. (See Page 7, lines 8 to 15.) Further, the radiation source is disposed completely within the expandable surface and is spaced apart from the apparatus volume. (See Page 8, line 23 to page 9 line 13, noting the

advantages of providing the radiation source within the interstitial volume and spaced apart from the target tissue; See also each of FIGS. 1 and 3 through 9, showing the radiation sources disposed entirely within the expandable surface). Further with respect to claim 1, the radiation source is located and arranged within the expandable outer surface so as to create asymmetric radiation isodose curves with respect to the apparatus volume. (See Page 9, line 23 to page 10, line 7.) That is, the radiation source is arranged within the device so that asymmetric dosing appears at the apparatus volume, which is configured to correspond to the interstitial void created by surgical extraction of diseased tissue.

The device of McGrath is not configured for use interstitially, it is configured for use interluminally, with balloons provided only to hold its catheter within a lumen, or to dialate the lumen. Accordingly, the radiation source in McGrath is not located completely within any of the disclosed balloons, nor is it located and arranged to provide an asymmetric dose at an apparatus volume that conforms to an interstitial void. Rather, McGrath provides an x-ray tube 48 that slides within a catheter, or a plurality of radiation-emitting seeds 52 "essentially forming a linear source." (Column 5, lines 34 to 37.) Accordingly, McGrath lacks several of the features recited in claim 1.

McGrath also lacks the features recited in claim 8 which depends from claim 1. Claim 8 recites that the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth. That is, the expandable outer surface actually causes the interstitial void to take on the same shape as the apparatus volume so that, even for oddly shaped voids in soft tissue, the shape of the target tissue that is to receive the asymmetric radiation dose will be the same as for the apparatus volume, enabling precise delivery of prescription doses of radiation asymmetrically from Applicants' claimed configuration.

As described above, McGrath does not disclose, teach or suggest the configuration that is recited in claim 9 that is also recited in claim 1. In addition to the structure it recites in common with claim 1, claim 9 recites an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with

respect to the apparatus volume. No portion of McGrath provides an outer expandable surface defining such an apparatus volume, and, while other configurations are referred to generically, the shielding that is provided by McGrath is simply a tubular shield that protects the bladder neck and sphincter. (See, Column 10, lines 7 to 39.) Nowhere does McGrath disclose, teach or suggest providing asymmetric shielding spaced apart from a radiation source so as to create predetermined asymmetric isodose curves with respect to an apparatus volume defined by the outer expandable surface.

Claim Rejections Over Ciezki in view of Apple

Claims 1 and 8 to 14 stand rejected as unpatentable over Ciezki (EP 0 867 200) in view of Apple (WO 99/33515) under 35 U.S.C. § 103. In particular, the Examiner states that:

> Ciezki et al teaches a treatment device having a plurality of radiation sources disposed in a catheter. Ciezki et al also teaches the use of shielding or an attenuator made from a radio-opaque material i.e. tantalum. Ciezki et al teaches the claimed device except for the use of an inflatable balloon catheter or the specific use of barium as the shielding material. Apple et al teaches a radioactive treatment device that uses an inflatable balloon to place the catheter at the treatment site. . . . Therefore a modification of Ciezki et al such that the catheter includes an inflatable balloon would have been obvious to help in the placement and retention of the catheter at the treatment site;

The combination of Ciezki and Apple suffers from all of the same problems as McGrath does. Regarding claim 1, the Examiner recognizes that Ciezki does not provide an expandable outer surface defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated; and a radiation source disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume. Apple does not fill in this missing teaching. Apple is directed to a catheter apparatus that is filled with a radioactive gas. The catheter can be used to treat restenosis after angioplasty, or it can treat malignancies. The "restenosis" configuration includes a number of balloons of the type generally used to hold a catheter in an artery; that is, interlumenally. None of these balloons define an apparatus volume within an interstitial void within which the radioactive source is completely placed. Even where Apple discloses a device for interstitial use (See, e.g., FIGS. 17 to 19), the radiation source completely fills the balloon and is not in a spaced apart relationship from the balloon as is recited in claim 1. Thus, even if a balloon from Apple were added to Ciezki, the configuration of claim

I would not result.

More significantly, neither Apple nor Ciezki nor their combination teaches asymmetric placement of a radiation source that is completely within an expandable surface defining an apparatus volume so as to result in asymmetric radiation isodose curves with respect to the apparatus volume. As described above and in the portions of the application cited above, Applicants' configuration provides significant advantages in the treatment of marginal proliferative tissue surrounding an interstitial void left by a surgical tumor resection. Accordingly, neither Ciezki nor Apple nor their combination renders the subject matter of claim 1 unpatentable to Applicants. Claim 8, which depends from claim 1, is further patentable over Ciezki and Apple because neither teaches or suggests the recitations of claim 8 for the same reasons as described above with respect to McGrath.

As described above, neither Ciezki nor Apple nor their combination discloses, teaches or suggests the configuration that is recited in claim 9 that is also recited in claim 1 – that is, an expandable outer surface having a base and defining a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated; and a radiation source disposed completely within and spaced apart from the expandable outer surface.

In addition to the structure it recites in common with claim 1, claim 9 recites an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves with respect to the apparatus volume. No portion of Ciezki defines such an apparatus volume and the only embodiment of Apple that provides an apparatus volume (FIGS 17 to 19) does not include any shielding. Where Ciezki and Apple do provide shielding, it is to protect blood flowing through the apparatus as it irradiates an aterial wall. The disclosed shielding does not provide asymmetric radiation dosing with respect to an expandable outer surface defining an apparatus volume, because there is no such volume in these references. As described above and in the portions of the application cited above, Applicants' configuration with asymmetric shielding provides significant advantages in that it provides precise delivery of prescription doses of radiation asymmetrically about an interstitial void created by surgical resection of diseased tissue. Neither of these references, alone or

combined, teach or suggest a device that achieves this result.

Conclusion

For all of the foregoing reasons, Applicants request that the Examiner reconsider the application and allow each of claims 1 to 14 to issue. If the Examiner believes that an interview would facilitate the resolution of any outstanding issues, the Examiner is kindly requested to contact the undersigned.

Dated: 2/27/02

Respectfully submitted,

By _____

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Complete Set of Pending Claims With Markings to Show Amendments Made

1. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface defining [an] a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source [replaceably disposable] disposed completely within the expandable outer surface and located so as to be spaced apart from the apparatus volume, the radiation source [comprising a plurality of solid radiation sources arranged] further being asymmetrically located and arranged within the expandable surface to provide predetermined asymmetric isodose curves [within the target tissue] with respect to the apparatus volume.

2. [The apparatus of claim 1, wherein a] A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of solid radiation sources [are] being provided in a spaced apart relationship on a single elongate member, the single elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources with respect to a longitudinal axis through the apparatus volume.

3. The apparatus of claim 2, further comprising a catheter in communication with the apparatus volume, the elongate member extending through the catheter into the apparatus volume.

4. The apparatus of claim 3, wherein the elongate member is formed of a shape memory alloy, the elongate member being shaped to provide asymmetric placement of the spaced apart solid radiation sources, taking on a substantially straight shape while being inserted through the

catheter to the apparatus volume, and resuming an asymmetric shape when extended into the apparatus volume.

5. [The apparatus of claim 1,] A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, wherein at least one of the plurality of solid radiation sources has a different specific activity from at least one other solid radiation source.

6. [The apparatus of claim 1, wherein] A surgical apparatus for providing radiation treatment to target tissue comprising:

an expandable outer surface defining an apparatus volume;

a radiation source replaceably disposable within the expandable outer surface, the radiation source comprising a plurality of solid radiation sources arranged to provide predetermined asymmetric isodose curves within the target tissue, the plurality of radiation sources [are] being provided on at least two elongate members extending into the apparatus volume, at least one of the elongate members being shaped to provide asymmetric placement of a radiation source with respect to a longitudinal axis through the apparatus volume.

7. The apparatus of claim 6, wherein each of the at least two elongate members includes a plurality of solid radiation sources provided in a spaced apart relationship.

8. The apparatus of claim 1, wherein the expandable outer surface is sufficiently rigid to deform the target tissue into the shape of the expandable outer surface, causing the predetermined asymmetric isodose curves to penetrate into the target tissue to a prescribed depth.

9. An interstitial brachytherapy apparatus for treating target tissue surrounding a surgical extraction comprising:

an expandable outer surface having a base and defining [an] a three-dimensional apparatus volume configured to fill an interstitial void created by the surgical extraction of diseased tissue and define an inner boundary of the target tissue being treated;

a radiation source [replaceably disposable] disposed completely within and spaced apart from the expandable outer surface; and

an asymmetric radiation shield spaced apart from the radiation source, the asymmetric radiation shield providing predetermined asymmetric isodose curves [within the target tissue] with respect to the apparatus volume.

10. The apparatus of claim 9, wherein the asymmetric radiation shield comprises a radio-opaque material disposed on only a portion of the expandable outer surface.

11. The apparatus of claim 10, wherein the expandable outer surface comprises an inflatable balloon.

12. The apparatus of claim 11, wherein the radiation shield comprises a barium material disposed a portion of the inflatable balloon.

13. The apparatus of claim 9, further comprising at least one radiation shield extending from the base of the expandable outer surface toward an opposite end of the expandable surface, the shield being in between and spaced apart from the radiation source and the expandable outer surface, the shield forming a radio-opaque barrier between a portion of the radiation source and the target tissue.

14. The apparatus of claim 13, wherein the radiation shield comprises two shields provided on opposite sides of the radiation source.

15. Canceled.

16. Canceled.

17. Canceled.

18. Canceled.

19. Canceled.

Exhibit 13

US005931774A

United States Patent [19]

Williams et al.

[11] **Patent Number: 5,931,774**

[45] **Date of Patent: Aug. 3, 1999**

[54] **INFLATABLE DEVICES FOR TUMOR TREATMENT**

[75] Inventors: **Jeffery A. Williams**, Baltimore, Md.; **Christopher H. Porter**, Woodinville, Wash.; **Mark A. Rydell**, Golden Valley, Minn.

[73] Assignee: **Proxima Therapeutics, Inc.**, Alpharetta, Ga.

[21] Appl. No.: **08/727,259**

[22] Filed: **Oct. 7, 1996**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/307,165, Sep. 14, 1994, Pat. No. 5,611,767, which is a continuation of application No. 07/715,923, Jun. 14, 1991, Pat. No. 5,429,582.

[51] **Int. Cl.**^{6} **A61N 5/02**

[52] **U.S. Cl.** **600/2**

[58] **Field of Search** 600/1–8; 604/19–20; 607/1–3, 88, 96, 99, 100, 103, 105, 107, 113, 114

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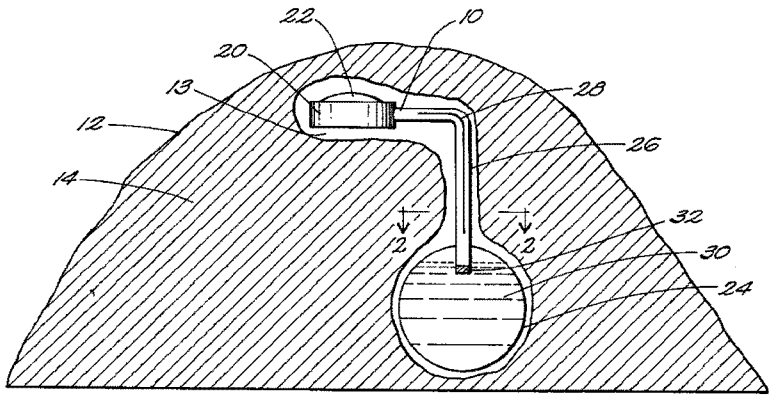
Primary Examiner—John P. Lacyk

Attorney, Agent, or Firm—Thomas J. Engellenner; Nutter, McClennen & Fish,LLP

[57] **ABSTRACT**

Implantable devices for treatment of proliferative disorders are described. In one aspect, the invention provides an implantable apparatus for treating a proliferative disorder in a patient. The device comprises a treatment fluid receptacle for receiving a treatment fluid, an inflatable balloon having a balloon body, a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween, and a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon. Methods for treating proliferative disorders with the devices are also disclosed.

43 Claims, 2 Drawing Sheets



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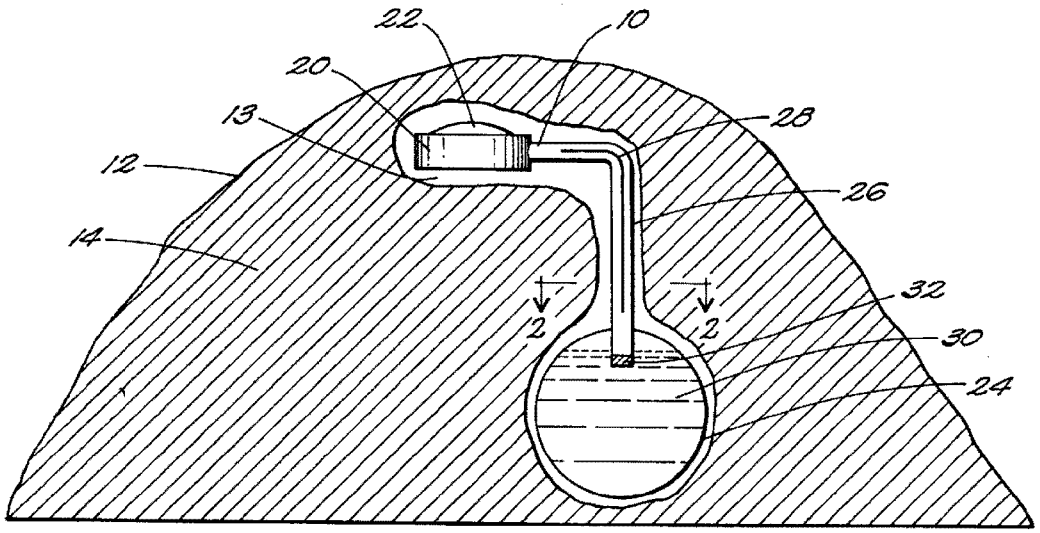


FIG. 1

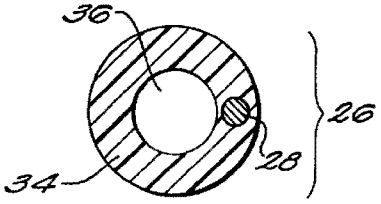


FIG. 2A

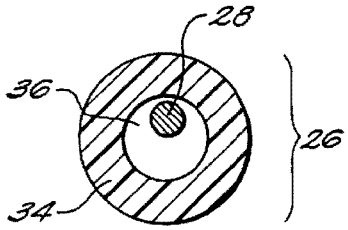


FIG. 2B

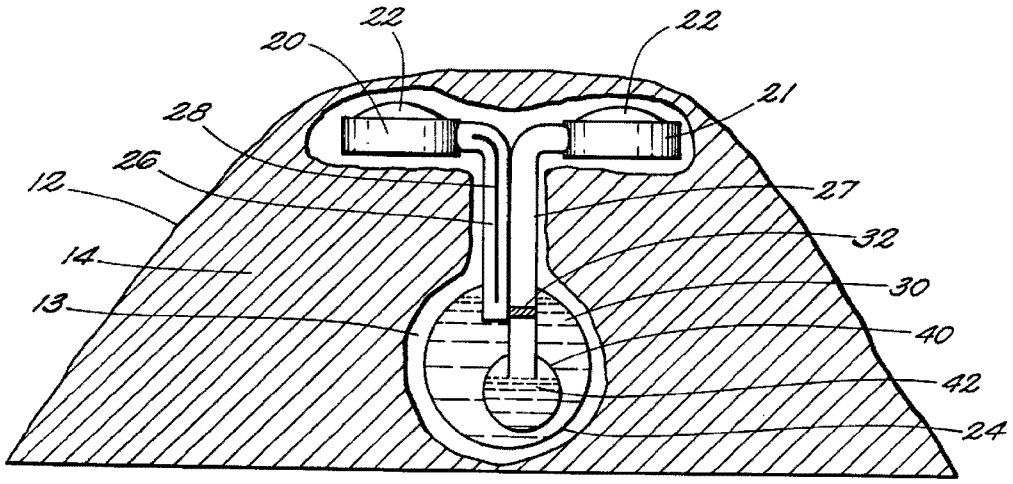


FIG. 3

INFLATABLE DEVICES FOR TUMOR TREATMENT

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08/307,165, filed Sep. 14, 1994, now U.S. Pat. No. 5,611,767, which is a continuation of U.S. Ser. No. 07/715,923, filed Jun. 14, 1991, now U.S. Pat. No. 5,429,582, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Treatment of proliferative disorders has become increasingly sophisticated in recent years, and improvements in surgical, chemotherapeutic and brachytherapeutic techniques have led to better outcomes in patients suffering from such disorders. The need for improved devices for administration of chemotherapy and brachytherapy has resulted in a number of new devices capable of delivering one or more treatments to proliferative disease sites, such as tumors. One such device is described in U.S. Pat. No. 5,429,582 to Williams, which discloses an inflatable device for multimodal therapy of tumors. Nevertheless, improved devices for treatment of proliferative disorders are needed.

SUMMARY

This invention provides improved devices for the treatment of tumors and other proliferative disorders in a patient in need of such treatment, and methods of treating proliferative disorders using such devices.

In one aspect, the invention provides an implantable apparatus for treating a proliferative disorder in a patient. The device comprises a treatment fluid receptacle for receiving a treatment fluid, an inflatable balloon having a balloon body, a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween, and a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon.

In certain embodiments, the treatment fluid receptacle has a small volume and is adapted to be implanted subcutaneously in the body of the patient. In certain embodiments, the device further includes a malleable element. In certain embodiments, the diffusion barrier is a narrow flow segment. In certain embodiments, the balloon has a substantially spherical shape when inflated. In other embodiments, the balloon has a substantially ovoid shape when inflated. In some embodiments, the balloon is secured to the catheter at substantially a single point on the balloon body. In other embodiments, the balloon is secured to the catheter at a plurality of points on the balloon body. In certain embodiments, the balloon has an irregular shape when inflated.

The balloon body can be substantially impermeable to the treatment fluid, while in other embodiments, the balloon can comprise a semipermeable membrane. In certain embodiments, the treatment fluid receptacle can be flushed with a flushing fluid without substantially expanding the balloon. In some embodiments, the balloon is secured to the catheter such that the balloon maintains a pre-selected shape during inflation. In preferred embodiments, the malleable element, if present, does not interfere with NMR measurements.

In certain embodiments, the balloon comprises a double-walled balloon or a triple-walled balloon. In some embodiments, the proliferative disorder is a brain tumor. In certain embodiments, the balloon is adapted for placement in a cavity left by surgical removal of a tumor from the patient. In other embodiments, the balloon is adapted for placement in a natural body cavity. In preferred embodiments, the balloon is filled with a treatment fluid. In certain embodiments, the treatment fluid is a radioactive fluid. In some embodiments, the treatment fluid has substantially physiological tonicity.

In certain embodiments, the apparatus further comprises a second treatment fluid receptacle. In certain embodiments, the second treatment fluid receptacle fluidly communicates with a volume between inner and outer balloon walls.

In another embodiment, the invention provides an implantable apparatus for treating a proliferative disorder in a patient. The implantable apparatus includes a treatment fluid receptacle for receiving a treatment fluid, an inflatable balloon having a balloon body; a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon, and in which the balloon is secured to the catheter such that the balloon maintains a pre-selected shape during inflation; and in which the treatment fluid receptacle is adapted to be flushed with a small volume of a flush fluid.

In another aspect, the invention provides a method for treating a proliferative disorder, such as a tumor, in a patient. The method includes the steps of implanting in the patient's body an inflatable treatment apparatus, in which the apparatus includes a treatment fluid receptacle for receiving a treatment fluid; an inflatable balloon having a balloon body; a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon; and introducing a treatment fluid into the treatment fluid receptacle such that the balloon is inflated; such that the proliferative disorder is treated.

In certain embodiments, the method includes the further step of flushing the treatment fluid into the balloon.

In another aspect, the invention provides a method for treating a proliferative disorder in a patient. The method comprises determining a characteristic of a cavity in the patient's body, the characteristic being selected from the group consisting of volume, shape, or a dimension; selecting an inflatable balloon suitable for placement in the cavity, the balloon including a balloon body. The method includes the further steps of implanting in the cavity an inflatable treatment apparatus comprising a treatment fluid receptacle for receiving a treatment fluid; the inflatable balloon; a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon. The method further includes the step of introducing a treatment fluid into the treatment fluid receptacle such that the balloon is inflated, such that the proliferative disorder is treated.

In certain embodiments, the method includes, prior to the implanting step, the further step of assembling the inflatable treatment apparatus.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic cross-sectional view of one embodiment of the treatment devices of the invention.

FIGS. **2**A and **2**B show cross-sectional views along the line **2**—**2**' of embodiments of the catheter of the invention.

FIG. **3** is a schematic cross-sectional view of a double-balloon embodiment of a treatment device of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The ability to selectively deliver therapy to a target organ or site, e.g., a tumor, is of great value to physicians. Accordingly, the invention provides methods and apparatuses suitable for delivery of one or more therapeutic modalities in a selective fashion.

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The term "proliferative disorder" is recognized in the art, and, as used herein, refers to a disorder including or characterized by rapid or abnormal cell growth or proliferation. Exemplary proliferative disorders include, but are not limited to, tumors, e.g., cancerous tumors; restenosis, e.g., regrowth of smooth muscle cells of blood vessels after angioplasty; abnormal angiogenesis; hyperplasia, e.g., benign prostatic hyperplasia; and the like.

The term "treatment fluid," as used herein, refers to a fluid used for therapy of a proliferative disorder. Treatment fluids include chemotherapy fluids such as are conventional in the art, as well as fluids suitable for radiation therapy (brachytherapy), e.g., fluids comprising a radioisotope useful in treatment of proliferative disorders.

The term "treatment fluid receptacle," as used herein, refers to a receptacle or chamber adapted for receiving a treatment fluid. Treatment fluid receptacles are known in the art, and include injection ports and similar devices. A "small-volume" treatment fluid receptacle has a volume or hold-up less than conventional treatment fluid receptacles, e.g., less than about 5 ml, more preferably less than about 2 ml, and still more preferably less than 1.5 ml. Thus, treatment fluid receptacles having little dead space or low hold-up volumes are generally preferred for use in the methods and devices of the invention. Particularly preferred treatment fluid receptacles can be flushed with a small volume of flush fluid, as described in more detail below.

The term "diffusion barrier," as used herein, refers to an element adapted for decreasing or preventing diffusion or flow of fluid from a balloon into the catheter lumen or treatment fluid receptacle of the subject inflatable treatment device.

A balloon that maintains a "substantially constant shape," as used herein, refers to a balloon that maintains substantially a single shape or profile over a range of inflation sizes. Thus, for example, a balloon that maintains a substantially spherical shape upon inflation has a generally spherical shape over a range of inflation sizes, from low inflation to full inflation, and does not generally change shape as inflation is increased or decreased. It will be understood by the skilled artisan, however, that the initial shape of a balloon can be chosen to minimize the size or profile of the deflated balloon, e.g., to ease insertion of the balloon into a body cavity. Thus, a balloon can have an initial shape different from a "substantially constant shape," and still assume a "constant shape" after partial inflation. A "predetermined shape" refers to a shape that can be selected by the practitioner before balloon insertion, e.g., a shape chosen to ensure compliance of the balloon body to a selected surface, e.g., a cavity surface.

The term "narrow flow segment", as used herein, refers to a narrowed or restricted portion of a flow path. Preferably, a narrow flow segment has a flow passage sufficiently small to slow or prevent significant flow or diffusion of a fluid through the passage without application of pressure.

The term "malleable element," as used herein, refers to an element, e.g., a wire, that is malleable or flexible, i.e., capable of being shaped by bending, flexing, pressing and the like, and maintaining, temporarily or permanently, the shape thus provided. In preferred embodiments, a malleable element can be shaped by hand, e.g., by a surgeon performing a surgical procedure, to impart a selected shape to the malleable element and to the catheter of which it forms a part.

The term "flushing fluid," as used herein, refers to fluid that can be used to flush, rinse, or wash a flow portion of an inflatable treatment device. A flushing fluid can be inert, e.g., a saline solution, or can itself be a treatment fluid. In general, an inert flushing fluid is preferred.

The term "patient," as used herein, refers to an animal in need of treatment for, or susceptible to, a proliferative disorder. In preferred embodiments, the patient is a warm-blooded animal, more preferably a mammal, including humans and non-human mammals such as dogs, cats, pigs, cows, sheep, goats, rats, and mice. In a particularly preferred embodiment, the subject is a human.

The inflatable treatment devices of the invention provide certain advantages over devices known in the art. The subject devices are adaptable to a wide variety of therapeutic treatments, and are simple and safe to use. In general, the devices are implanted in a patient's body such that the balloon is in close proximity to the site to be treated, e.g., the tumor, blood vessel, and the like. In one embodiment, the balloon is placed in a natural body cavity or a cavity resulting from surgical removal or displacement of tissue, e.g., surgical debulking of at least a portion of a tumor, or angioplasty to displace or compress a growth of a blood vessel.

Thus, for example, FIG. **1** shows a cross-sectional view of an inflatable device of the invention when implanted in a body cavity. In this embodiment, the device **10** is implanted below the skin **12** in a cavity **13** formed in the patient's tissue **14**. The device **10** includes an injection port **20** which has an elastomeric seal **22** secured thereto. A balloon **24** is disposed in the cavity **13** and fluidly connected to the injection port **20** through a catheter **26**, which includes a malleable element **28**. The balloon is filled with a treatment fluid **30**, which fluid is prevented from flowing back from the balloon **24** into the catheter **26** by a diffusion barrier **32**.

In certain embodiments, a treatment fluid receptacle is implanted subcutaneously, permitting ready injection of a treatment fluid while allowing healing of a surgical incision. Treatment fluid receptacles suitable for use in the devices of the invention are known in the art. For example, injection ports, which can be subcutaneously implanted, have been described in, e.g., U.S. Pat. Nos. 4,816,016 and 4,681,560 to Schulte, and are commercially available (e.g., from C. R. Bard Co.). An injection port for implantation in vivo should be constructed of materials that will not provoke an immune response or tissue reaction. An injection port preferably has an elastomeric seal secured to a base and defining an injection chamber of predetermined volume. The elastomeric seal can be adapted to sealingly engage a needle that pierces the seal, e.g., a hypodermic needle, and to reseal when the needle is removed, thereby preventing leakage. In general, preferred treatment fluid receptacles can be readily and efficiently flushed with a small volume of flush fluid, e.g., can be flushed with less than about 5 ml of flush fluid, more preferably less than about 2 ml, and still more pref-

erably less than 1.5 ml. The amount of flush fluid required will be determined, at least in part, by such factors as the total volume of the treatment fluid receptacle, the amount of "dead space" in the treatment fluid receptacle, the nature of the treatment fluid and the flush fluid, and the like. In preferred embodiments, the volume of the treatment fluid receptacle, e.g., the injection chamber, is minimized, e.g., has a small volume. By providing a small-volume treatment fluid receptacle, the volume of treatment and flushing fluids is minimized, preventing overinflation of the balloon and decreasing the volume of fluids that must be handled by the physician. Preferred treatment fluid receptacles have a volume of at least 0.5 ml, but not more than 5 ml, more preferably between about 1 and about 3 ml. In general, it is desirable for the injection port to be palpable through the skin, so that it can be easily located. The treatment fluid receptacle can be at least partially opaque to X-rays, permitting localization by radiography.

As mentioned above, in certain embodiments it is desirable, after treatment fluid has been injected into the treatment device, to flush the injection port to displace a treatment fluid from the injection port and catheter. For example, when the treatment fluid is a radioactive fluid, it is desirable to prevent radiation damage to healthy tissue adjacent to the treatment fluid receptacle and along the catheter path. To prevent damage to healthy tissue, the treatment fluid can be flushed out of the injection port and away from such tissue. The flush fluid can be flushed through the catheter and into the balloon, thereby flushing the catheter and increasing the amount of radioactive material in the balloon. A small-volume treatment fluid receptacle can be flushed rapidly and completely using small volumes of flush solution, thereby reducing the amount of additional fluid added to the balloon. Thus, a small-volume treatment fluid receptacle is preferred for use with radioactive treatment fluids. Alternatively, the flush fluid can be removed from the treatment device, e.g., by use of a needle, positioned in the injection port, for withdrawing excess fluid. In this embodiment, two needles can be employed simultaneously: one needle for injection of a flush fluid into the injection port, and a second needle for removal of the fluid. In this embodiment, further inflation of the balloon can be prevented.

The inventive devices can include a diffusion barrier, to prevent unwanted backflow of treatment fluid from the balloon into the catheter. The diffusion barrier thereby prevents premature deflation of the balloon and isolates the treatment fluid in the balloon. In particular, the diffusion barrier can reduce or prevent diffusion or flow of a treatment fluid, especially a radioactive treatment fluid, from the balloon into the catheter or other parts of the implantable device, thereby preventing damage to healthy tissue adjacent to the catheter track. The diffusion barrier can be any element or elements adapted to retard or prevent fluid flow, including, without limitation, a valve (e.g., a check valve) or other flow regulating element, a narrow flow segment, and the like. A valve can be manually or automatically operated to permit control of fluid flow, if desired, e.g., during balloon filling, flushing of an injection port, or removal of fluid from the device. In certain embodiments, the diffusion barrier is an elastomeric material disposed in the fluid flow path and having a slit, e.g., a slit of proportions similar to a Holter valve opening. In this embodiment, fluid flow through the diffusion barrier can be accomplished by the application of fluid under pressure, e.g., by providing a fluid under pressure with a hypodermic syringe, causing the elastomer to yield sufficiently to permit fluid flow. Preferably, the pressure required to cause fluid flow through the diffusion barrier is not so high as to present risk of rupture of the therapeutic device, but is sufficient to reduce unwanted flow from the balloon. The diffusion barrier can provide resistance to fluid flow in one direction (e.g., a one-way check valve) or in both directions. However, the diffusion barrier is preferably adapted to allow removal of fluid from the balloon when the therapeutic procedure is complete, preferably without requiring removal of the balloon from the body cavity. Thus, in certain embodiments, the diffusion barrier is not a check valve. The diffusion barrier can reduce or eliminate flow from the balloon for at least a short period of time, e.g., sufficient time for therapeutic treatment to be completed.

In certain embodiments, the inventive apparatus can include a malleable element extending through at least a portion of the length of the catheter lumen. Thus, the malleable element is preferably adapted to confer a shape upon at least a portion of the catheter length. The malleable element is preferably an integral component of the catheter, and is not a stylet or guidewire. The malleable element can provide increased stiffness to the catheter, thereby preventing kinking of the catheter and concomitant blockage of the lumen, during insertion or removal. In particular, the malleable element can eliminate the need for a separate guidewire or stylet for inserting the catheter, simplifying surgical procedures. However, the malleable element should not be excessively rigid, to avoid damaging fragile tissues. The malleable element further can permit a shape to be temporarily or permanently imparted to the catheter. Thus, the catheter can be easily and accurately placed in the patient's body. For example, the malleable element can be conformed to a shape of a body lumen, or can be formed to permit the balloon to be placed at a body site not readily accessible by conventional means. Also, the malleable element can provide a means for securing or anchoring the implantable device in a patient's body and preventing the catheter from "backing out" during or after surgical placement.

The malleable element can comprise, a flexible wire, which can be embedded in a wall of the catheter, secured to an inner or outer surface of a sidewall of the catheter, or can be situated in the lumen of the catheter. Thus, for example, FIG. **2**A depicts a cross-sectional view of one embodiment of a catheter along line **2**—**2** of FIG. **1**. The sidewall **34** of the catheter **26** defines a catheter lumen **36**. A malleable wire **28** is embedded in the sidewall **34**. FIG. **2**B depicts a catheter in which a malleable element **28** is secured to the sidewall **34** in the catheter lumen **36** of catheter **26**. The wire can be made of, stainless steel, titanium and other metals, and alloys thereof. A preferred malleable element is a titanium wire, e.g., a 20 mil annealed titanium wire. In one embodiment, the malleable element comprises a metallic element or alloy, such as nitinol, which exhibits "shape memory," i.e., has the property of returning to a predefined shape upon heating. In this embodiment, the wire can be selected to have a desired shape when implanted, but can be bent to a different shape prior to insertion to accommodate placement in vivo, and then heated (e.g., with a resistive heater) to restore the preselected shape. In certain preferred embodiments, the malleable element comprises a metallic element or alloy which does not substantially interfere with NMR measurements, e.g., magnetic resonance imaging; i.e., NMR measurements of the patient's body can be performed while the malleable element is present in the patient's body. In this embodiment, non-ferromagnetic metals or alloys are preferred. A preferred malleable element comprises an annealed titanium wire, preferably about 20 mil in diameter.

Such a wire can also be employed to provide a source of electric current, e.g., to a resistive heater, or to provide means for monitoring conditions, e.g., temperature, inside the patient's body. Thus, a malleable wire can provide means for additional treatment modalities, e.g., heat therapy, which can be employed in conjunction with chemotherapy and brachytherapy, if desired. Additionally, the malleable element can be employed as a radio-opaque marker for locating the catheter in the body.

The inflatable treatment devices include an inflatable balloon for containing a treatment fluid in close proximity to the tissue to be treated. It will be understood that the term "balloon" is intended to include distensible devices which can be, but need not be, constructed of an elastic material. A variety of balloons or other distensible devices for use with surgical catheters are known in the art and are contemplated for use in the invention; many balloons are commercially available. In one embodiment, the balloon is constructed of a material that is substantially impermeable to the active components of the treatment fluid with which it is filled, and is also impermeable to body fluids, e.g., blood, cerebrospinal fluid, and the like. An impermeable balloon is useful in conjunction with a radioactive treatment fluid, to prevent the radioactive material from escaping the treatment device and contaminating the surgical field or tissues of the patient. In another embodiment, the balloon is permeable to the treatment fluid, and permits the fluid to pass out of the treatment device and into a body lumen or cavity. A permeable balloon is useful when the treatment fluid is a chemotherapeutic agent which must contact tissue to be effective. Semi-permeable balloons can also find use in the inventive devices. For example, a semipermeable material that is capable of preventing the passage of a radioactive material through the balloon wall can be used to contain a radioactive treatment fluid, where certain fluid components can pass through the membrane while the radioactive component is retained within the balloon. In some embodiments, isotonic fluids are preferred for use in semipermeable balloons, as discussed below. Silicone, e.g., NuSil, is a preferred material for a balloon wall.

In general, it is preferable that the balloon have a shape that permits the balloon to conform to the body cavity or lumen in which the balloon is to be inflated. For example, a generally spherical cavity can be filled with a substantially spherical balloon, while an elongated balloon shape is suitable for an elongated body lumen such as a blood vessel. Irregular balloon shapes may also find application in the subject devices and methods. In certain embodiments, a balloon will be selected such that, upon inflation, the balloon does not compress the tissue which is being treated, or surrounding tissues. Thus, when a radioactive treatment fluid is introduced into the device, e.g., by injection, the inflatable treatment device is inflated to a volume not substantially greater than a volume of the body cavity in which the device has been placed, thereby avoiding any substantial compression or distortion of normal tissue. For example, in one embodiment, when the balloon is placed within a cavity left by surgical removal of tissue, the balloon is not inflated to a size substantially larger than the size of the cavity. However, in certain embodiments, the balloon preferably is inflated to compress tissue. For example, when the proliferative disorder being treated is, e.g., restenosis of a blood vessel, the balloon can be inflated to a size large enough to compress the excess tissue, while also providing chemotherapy, brachytherapy, or the like to treat the lesion. Thus, a balloon can be selected to have a desired size, and the amount of treatment fluid can be adjusted to attain an inflation of the balloon to achieve the desired size. In general, the balloon should have a small profile, e.g., a small size, when deflated, to permit facile placement in the patient's body and to minimize the size of a surgical incision needed to place the balloon at the desired site of action.

In some embodiments, a balloon is attached to the catheter at substantially a single point on, or a single side of, the balloon body. Catheters suitable for use in the invention are well known in the art. A preferred catheter material is radio-opaque silicone. Attachment of a balloon to a catheter at a single point on the balloon body permits the balloon (e.g., a spherical balloon) to maintain a substantially constant (e.g., spherical) shape over a range of inflation volumes. That is, the balloon is not constrained in shape by multiple attachment points to the catheter, as is commonly the case with, e.g., balloons for Foley catheters. In other embodiments, the balloon is attached to the catheter at multiple points on the balloon body, while allowing the balloon to maintain a constant shape over a range of inflation sizes. For example, a balloon attached to a catheter at both distal and proximal points on the balloon body can be unconstrained upon inflation where the catheter includes an expansion element (e.g., a slidable engagement element) that permits the catheter to adjust in length as the balloon expands or contracts. A balloon which maintains a substantially constant shape over a range of inflation volumes permits a surgeon to select a balloon to conform to a cavity of a particular shape with less concern over the size of the cavity. Thus, devices that include such a balloon reduce the need for the surgeon to prepare several different-sized balloons prior to surgery.

The invention also contemplates the use of multiple balloons, e.g., a double-walled balloon. Such a balloon can comprise, for example, an impermeable inner wall and a permeable outer wall. In this embodiment, the inner balloon can be filled with, e.g., a radioactive treatment fluid, while the outer balloon (i.e., the space between the inner and outer balloon walls) is filled with a chemotherapeutic treatment fluid. This embodiment allows two modes of therapy (e.g., chemotherapy and brachytherapy) to be administered simultaneously with a single device. In this double-walled balloon embodiment, the device preferably includes two treatment fluid receptacles, one in communication with each of the two balloons, preferably through a separate catheter, one catheter fluidly connected to each balloon and treatment fluid receptacle. The two balloons can thus be inflated with two treatment fluids at the same time or at different times during therapy. Inflation of an inner balloon can provide pressure on an outer balloon, which can cause the outer balloon to expand, or can force or urge fluid in the space between the inner and outer balloon walls through the membrane of a porous outer balloon. Higher-order balloons, e.g., triple-walled balloons, can also be used in the inventive devices.

Thus, for example, FIG. **3** shows a double-balloon device of the invention. The device has two treatment fluid receptacles **20**, **21**, each having an elastomeric seal **22** secured thereto. Receptacle **20** is fluidly connected to outer balloon **24** through catheter **26**, which includes a malleable element **28**, and receptacle **21** is fluidly connected to inner balloon **40** by catheter **27**, which includes diffusion barrier **32**. The device of FIG. **3** is useful where a chemotherapeutic fluid **30** is used to inflate the outer balloon **24**, while a radioactive fluid **42** fills the inner balloon **40**. Diffusion barrier **32** prevents flow of the radioactive fluid **42** from the balloon **40** to the catheter **27**.

The catheter element can be any of a variety of catheters known in the art. A preferred catheter material is silicone,

preferably a silicone that is at least partially radio-opaque, thus facilitating x-ray location of the catheter after implantation of the device. The catheter can also include conventional adapters for attachment to the treatment fluid receptacle and the balloon, as well as devices, e.g., right-angle devices, for conforming the catheter to contours of the patient's body.

In some embodiments, the inventive devices are provided in pre-assembled form, i.e., the components are assembled in advance of a surgical insertion procedure. In certain embodiments, however, the inventive devices are configured to permit modular assembly of components, e.g., by a surgeon. Thus, for example, a treatment fluid receptacle can be provided with an element adapted for connection to any one of a plurality of catheters. The connection element can be, e.g., any element known in the art for effecting connection between components such as catheters, injection ports, and the like. Illustrative connectors include luer adapters and the like. In this embodiment, a variety of catheters and balloons can be provided, each of which is adapted for facile connection to the treatment fluid receptacle. The surgeon can then select an appropriate size and shape of balloon for treatment of a particular proliferative disorder without need for providing several treatment fluid receptacles. The catheter and balloon can be selected according to the results of pre-operative tests (e.g., x-ray, MRI, and the like), or the selection can be made based on observation, during a surgical procedure, of the target cavity (e.g., a surgical cavity resulting from tumor excision). When the surgeon selects an appropriate balloon (e.g., a balloon having a size and shape suitable for placement in a body cavity), the catheter and balloon can then be attached to the pre-selected treatment fluid receptacle, thereby assembling the treatment device.

The above-described implantable inflatable treatment devices can be employed in the treatment of proliferative disorders in a patient. In one aspect, the invention provides a method of treating proliferative disorders including the step of implanting in the patient's body an inflatable treatment apparatus, in which the apparatus includes a small-volume treatment fluid receptacle for receiving a treatment fluid; an inflatable balloon having a balloon body; a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon; wherein the balloon is secured to the catheter such that the balloon maintains a substantially constant shape during inflation; and introducing a treatment fluid into the treatment fluid receptacle so that the balloon is inflated, such that the proliferative disorder is treated. In certain embodiments, the method includes the step of selecting a balloon for treatment a proliferative disorder in a patient. In some embodiments, the method includes, prior to the implanting step, the further step of assembling an inflatable treatment apparatus.

The treatment devices of the invention (or any part thereof, e.g., the balloon) can be implanted according to surgical methods well known to the skilled artisan. In one embodiment, the balloon is implanted in a cavity formed by removal of tissue from a tumor or organ. Thus, in certain embodiments, the method includes the step of surgically removing tissue to form a cavity in the patient's body prior to implanting the inflatable device. In other embodiments, the device is implanted in a natural body cavity, e.g., in the abdominal cavity, or an organ such as a lung, uterus, or prostate gland. In yet other embodiments, a cavity or space, for placement of the inventive device in a patient's body, can be formed by displacing, compressing, or otherwise repositioning tissue, without surgically removing tissue. Illustratively, tissue can be compressed, e.g., by inflation of a balloon, prior to placement of a device of the invention in the cavity formed thereby. In certain embodiments, the treatment fluid receptacle is implanted subcutaneously. It will be appreciated that the catheter or catheters of the device can be implanted so as to pass through a body wall, e.g., the skull, the abdominal wall, and the like.

The treatment fluid (or fluids) for inflating the balloon (or balloons) can be provided to the treatment fluid receptacle by, e.g., transcutaneous injection into an injection port(s). Injection can be with a syringe, e.g., a hypodermic syringe, or with a pump or other mechanical delivery means.

In certain preferred embodiments, the proliferative disorder is a tumor, more preferably a solid tumor, including both benign and malignant tumors. In some embodiments, the tumor is a cancerous tumor. Methods of the invention are useful in treating cancers such as, without limitation, brain tumors, breast tumors, prostate tumors, ovarian tumors, and the like. In another preferred embodiment, the proliferative disorder is restenosis, e.g., of a blood vessel. Thus, the subject method can be employed to treat or to prevent restenosis in a patient. Similarly, the subject method can be employed to treat hyperplasia, including endometriosis, benign prostatic hyperplasia, and the like.

In certain embodiments, the treatment fluid includes a chemotherapy agent. Formulation and dosage of chemotherapy agents is routine to the skilled artisan. In certain embodiments, the treatment fluid includes a radioisotope. Radioactive treatment fluids are useful for brachytherapy, as discussed supra. Preferred radioisotopes for brachytherapy include ^{90}Y, ^{198}Au, ^{32}P, ^{125}I, and ^{131}I. Radioisotope preparations suitable for use in the subject treatment devices are known to those of skill in the art. It will be appreciated that a treatment fluid can be formulated to provide more than one treatment modality. For example, a chemotherapy fluid can be heated to provide both chemotherapy and heat therapy. In certain embodiments, the treatment fluid is approximately isotonic with body fluids; that is, the tonicity (ionic strength) of the treatment fluid is close to that of physiological fluids. Use of isotonic treatment fluids avoids transfer of solutions across the balloon body membrane, thereby preventing unexpected or undesired inflation or deflation of the balloon, or dilution or concentration of the treatment fluid.

In certain embodiments, the method of treatment includes the further step of flushing the treatment fluid receptacle (e.g., the injection port) with a flush fluid. As previously described, it is important to avoid damaging healthy tissue by exposure to high doses of radiation from the treatment fluid. Thus, to prevent damage to tissue adjacent the injection port and the catheter, the injection port and catheter can be flushed with a non-radioactive flush fluid. In certain embodiments, the flush fluid is flushed into the balloon. In this embodiment, the volume of flush fluid should be carefully regulated to ensure that the balloon does not become overinflated. In certain embodiments, the flush fluid inflates the balloon by no more than 20%, more preferably no more than 10%. Alternatively, the flush fluid can be withdrawn from the treatment device, e.g., by removal with a needle introduced into the injection port. In this embodiment, the balloon is preferably not significantly further inflated, e.g., inflation due to the flush solution is less than 10%, more preferably less than 5%, of the volume of the inflated balloon. In some preferred embodiments, e.g., where a radioactive treatment fluid has been employed, the flushing step can reduce the level of radioactivity present in the

treatment fluid receptacle or the catheter by at least about 50%, more preferably by at least 80%, and still more preferably by at least 90%.

In certain embodiments, the flush solution has approximately physiological tonicity. In some embodiments, the flush solution is more viscous than the treatment fluid such that the flow of the flush fluid approaches plug flow. A viscous flush solution can also prevent backflow or diffusion of a radioactive treatment fluid because the higher viscosity impedes flow in the catheter lumen.

The treatment is preferably continued until the proliferative disorder has been significantly ameliorated, e.g., if the proliferative disorder is a tumor, treatment is continued until the tumor has decreased in size by at least about 10%, more preferably at least about 20%. The inflatable device can be left in place and repeated filled with treatment fluid, if desired. For example, repeated doses of a chemotherapy fluid can be administered without disturbing the placement of the device, simply by injecting more treatment fluid into a permeable balloon after-the original dose has passed through he balloon. Similarly, a radioactive fluid can be removed, e.g., to prevent excessive doses of radiation or when the radioisotope has decayed, and replenished by addition of fresh radioisotope solution. Where it is desired to use repeated doses, the strength of the doses can be varied, for example, a first, strong dose, followed by a second, less potent dose. Determination of appropriate dosages strengths and treatment regimens will be routine for the skilled artisan.

The contents of each patent, patent application, and publication cited herein are hereby incorporated by reference.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the methods and devices described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

What is claimed is:

1. An implantable apparatus for treating a proliferative disorder in a patient, comprising:

a treatment fluid receptacle for receiving a treatment fluid;

an inflatable balloon having a balloon body;

a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and

a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon.

2. The apparatus of claim **1**, wherein the treatment fluid receptacle has a small volume and is adapted to be implanted subcutaneously in the body of the patient.

3. The apparatus of claim **1**, wherein the diffusion barrier is a narrow flow segment.

4. The apparatus of claim **1**, wherein the balloon has a substantially spherical shape when inflated.

5. The apparatus of claim **1**, wherein the balloon is secured to the catheter at substantially a single point on the balloon body.

6. The apparatus of claim **1**, wherein the balloon is secured to the catheter at a plurality of points on the balloon body.

7. The apparatus of claim **1**, wherein the catheter further comprises a malleable element.

8. The apparatus of claim **1**, wherein the balloon body is substantially impermeable to the treatment fluid.

9. The apparatus of claim **1**, wherein the balloon comprises a semipermeable membrane.

10. The apparatus of claim **1**, wherein the treatment fluid receptacle is sized and dimensioned for being flushed with a flushing fluid without substantially expanding the balloon.

11. The apparatus of claim **1**, wherein the balloon is secured to the catheter such that the balloon maintains a pre-selected shape during inflation.

12. The apparatus of claim **1**, wherein the balloon comprises a double-walled balloon having an inner wall and an outer wall.

13. The apparatus of claim **1**, wherein the balloon is sized and dimensioned for placement in a blood vessel.

14. The apparatus of claim **1**, wherein the balloon is sized and dimensioned for placement in a cavity left by surgical removal of a tumor from the patient.

15. The apparatus of claim **1**, wherein the balloon is sized and dimensioned for placement in a natural body cavity.

16. The apparatus of claim **1**, wherein the balloon is filled with a treatment fluid.

17. The apparatus of claim **16**, wherein the treatment fluid is a radioactive fluid.

18. The apparatus of claim **16**, wherein the treatment fluid has substantially physiological tonicity.

19. The apparatus of claim **12**, further comprising a second treatment fluid receptacle.

20. The apparatus of claim **19**, wherein the second treatment fluid receptacle fluidly communicates with a volume between inner and outer balloon walls.

21. An implantable apparatus for treating a proliferative disorder in a patient, comprising:

a treatment fluid receptacle for receiving a treatment fluid;

an inflatable balloon having a balloon body; and

a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween;

wherein the catheter further comprises a malleable element.

22. The apparatus of claim **21**, wherein the malleable element does not substantially interfere with NMR analysis.

23. The apparatus of claim **21**, wherein the balloon is sized and dimensioned for placement in a blood vessel.

24. An implantable apparatus for treating a proliferative disorder in a patient, comprising:

a treatment fluid receptacle for receiving a treatment fluid;

an inflatable balloon having a balloon body;

a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and

a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon;

wherein the treatment fluid receptacle is adapted to be flushed with a small volume of a flush fluid.

25. A method for treating a proliferative disorder in a patient, the method comprising the steps of:

implanting in the patient's body an inflatable treatment apparatus, the apparatus comprising:

a treatment fluid receptacle for receiving a treatment fluid;

an inflatable balloon having a balloon body;

a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween; and

a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon; and

introducing a treatment fluid into the treatment fluid receptacle such that the balloon is inflated;

such that the proliferative disorder is treated.

26. The method of claim **25**, further comprising the step of flushing the treatment fluid into the balloon.

27. The method of claim **25**, wherein the treatment fluid is flushed into the balloon with a flush fluid.

28. The method of claim **27** wherein the flush fluid further inflates the balloon by no more than 10% of the balloon volume prior to the flushing step.

29. The method of claim **25**, wherein the implanting step comprises the step of positioning the inflatable balloon adjacent to a tumor.

30. The method of claim **29**, wherein the implanting step comprises the step of positioning the inflatable balloon adjacent to a solid tumor.

31. The method of claim **29**, wherein the implanting step comprises the step of positioning the inflatable balloon adjacent to a cancerous tumor.

32. The method of claim **29**, wherein the implanting step comprises the step of positioning the inflatable balloon adjacent to a brain tumor.

33. The method of claim **29**, wherein the implanting step comprises the step of positioning the inflatable balloon adjacent to a breast tumor.

34. The method of claim **25**, further comprising, prior to the implanting step, the step of surgically creating a cavity in the patient's body.

35. The method of claim **25**, further comprising, prior to the implanting step, the step of selecting a balloon for treating the proliferative disorder.

36. The method of claim **35**, further comprising, prior to the implanting step, the step of assembling the inflatable treatment apparatus.

37. The method of claim **25**, wherein the apparatus is implanted in a natural body cavity.

38. A method for treating a proliferative disorder in a patient, the method comprising:

determining a characteristic of a cavity in the patient's body, the characteristic being selected from the group consisting of volume, shape, or a dimension;

selecting an inflatable balloon suitable for placement in the cavity, the balloon including a balloon body;

implanting in the cavity an inflatable treatment apparatus comprising:

a treatment fluid receptacle for receiving a treatment fluid;

the inflatable balloon;

a catheter connected between the treatment fluid receptacle and the balloon and defining a fluid flow path therebetween;

a diffusion barrier disposed in the fluid flow path between the treatment fluid receptacle and the balloon; and

introducing a treatment fluid into the treatment fluid receptacle such that the balloon is inflated;

such that the proliferative disorder is treated.

39. The method of claim **38**, wherein the treatment fluid is a radioactive fluid.

40. The method of claim **38**, wherein the treatment fluid is a chemotherapy fluid.

41. The method of claim **38**, the method comprising, prior to the implanting step, the further step of assembling the inflatable treatment apparatus.

42. An implantable apparatus for treating a proliferative disorder in a patient, said apparatus comprising:

a treatment fluid receptacle for receiving a treatment fluid;

an inflatable balloon having a balloon body;

a catheter connected between said treatment fluid receptacle and said balloon, said catheter defining a fluid flow path therebetween; and

a narrow flow segment disposed in said fluid flow path between said treatment fluid receptacle and said balloon.

43. An implantable apparatus for treating a proliferative disorder in a patient, said apparatus comprising:

a treatment fluid receptacle for receiving a treatment fluid;

an inflatable balloon having a balloon body;

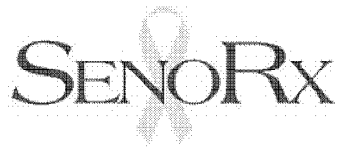
a catheter connected between said treatment fluid receptacle and said balloon, said catheter defining a fluid flow path therebetween;

a malleable element coupled to said catheter, and

a diffusion barrier disposed in the fluid flow path between said treatment fluid receptacle and said balloon.

* * * * *

Exhibit 16



A MULTI-SITE PROSPECTIVE, NON RANDOMIZED STUDY UTILIZING THE CONTURA™ MULTI-LUMEN BALLOON (MLB) BREAST BRACHYTHERAPY APPLICATOR TO DELIVER ACCELERATED PARTIAL BREAST IRRADIATION: ANALYSIS OF DOSIMETRIC SUCCESS, LOCAL TUMOR CONTROL, COSMETIC OUTCOME, ACUTE AND CHRONIC TOXICITY, AND CLINICAL SCENARIOS FOR OPTIMAL USE

PROTOCOL NO. S07-002

MARCH 6, 2008

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STUDY SYNOPSIS

Study Design

This multiple site, prospective, non-randomized study has been designed to compile information on the efficacy of the Contura™ MLB in delivering APBI in appropriately selected patients through evaluation of dosimetric success as compared with a single central lumen balloon device and through treatment outcomes.

Data collected during this study will include baseline patient demographics, information related to the time of implant, radiation therapy details, and removal of the device as well as recurrence data, cosmetic outcomes and toxicities. The patient's follow-up data will be collected during the patient's standard follow-up visits. The study will continue until 342 patients have been accrued and followed for 5 years.

Study Objectives

- To compare the dosimetric efficacy of the Contura™ MLB with the historical efficacy rate of a single central lumen balloon device.
- To quantify the dosimetric improvement of multi-lumen use over single lumen use through dosimetric comparison.
- To estimate the local tumor control rate in the breast (and regional and distant sites) with the Contura™ MLB to deliver APBI.
- To evaluate the cosmetic results in the breast utilizing the Contura™ MLB to deliver APBI.
- To evaluate treatment related toxicities in the breast utilizing the Contura™ MLB to deliver APBI (i.e., seroma formation, infection, fat necrosis, pain, telangiectasia, and pigmentation).
- To determine the frequency and type of clinical scenarios where only the Contura™ MLB could be safely used to deliver adjuvant APBI using balloon brachytherapy because of (a) skin spacing concerns, (b) sub-optimal balloon conformance to the lumpectomy cavity, (c) dosimetric limitations (i.e., radiation "hot spots" creating potential concerns such as fat necrosis or other late tissue toxicities), (d) normal tissue concerns (i.e., proximity to chest wall, heart, etc.), or (e) sub-optimal surgical margins requiring eccentric expansion of the full-dose radiation margin to cover any possible residual disease.

Primary Endpoint

To compare the success rate of the Contura™ MLB with a single central lumen balloon device. "Success" is defined as a combined criterion of meeting all of the following:

- Maximum total skin dose $\leq$ 125% of prescribed dose (i.e., 42.5 Gy)
- Maximum rib dose $\leq$ 145% of prescribed dose (i.e., 50 Gy)
- V 150 $\leq$ 50 cc
- V 200 $\leq$ 10 cc
- 95% coverage of target volume with $\geq$ 95% of prescribed dose with 5% relaxation of these stated boundaries

Secondary Endpoints

- Disease control (local ipsilateral, contralateral, regional, and distant recurrences)
- Cosmetic results
- Toxicity rates (seroma formation, infection, fat necrosis, pain, telangiectasia, and pigmentation)
- Clinical scenarios where only the Contura™ MLB could be safely used to deliver adjuvant APBI using balloon brachytherapy

Inclusion Criteria

- Able and willing to sign informed consent
- Age 50 or older at diagnosis
- Life expectancy greater than 10 years (excluding diagnosis of breast cancer)
- Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor (negative surgical margins per NSABP criteria).
- On histologic examination, the tumor must be DCIS and/or invasive breast carcinoma.
- For patients with invasive breast cancer, an axillary staging procedure must be performed [either SNB alone or axillary dissection (with a minimum of six axillary nodes removed), and the axillary node(s) must be pathologically negative].
- The T stage must be Tis, T1, or T2. If T2, the tumor must be ≤ 3.0 cm in maximum diameter.
- Estrogen receptor positive tumor

Exclusion Criteria

- Age < 50 at diagnosis (regardless of histology)
- Pregnant or breast-feeding
- Active collagen-vascular disease
- Paget's disease of the breast
- Prior history of DCIS or invasive breast cancer
- Prior breast or thoracic RT for any condition
- Multicentric carcinoma (DCIS or invasive)
- Synchronous bilateral invasive or non-invasive breast cancer
- Surgical margins that cannot be microscopically assessed or that are positive
- Positive axillary node(s)
- T stage of T2 with the tumor > 3 cm in maximum diameter or a T stage ≥ 3
- Estrogen receptor negative tumor

I. INTRODUCTION

Breast conserving therapy (BCT) has become an accepted option for most patients with stage I and stage II breast cancer and those with ductal carcinoma in-situ (DCIS) of the breast as well. Studies have shown BCT to be comparable to mastectomy in terms of overall and disease free survival (1, 2). The major advantages to BCT over mastectomy are an improved cosmetic outcome and reduced psychological trauma to the patient. One of the major disadvantages of BCT is the prolonged time of treatment. The radiation portion of BCT can add up to 6-7 weeks to the overall treatment time. This additional time can impose a significant burden for women who logistically may not be able to meet the demands of daily irradiation for over 6 weeks.

Accelerated partial breast irradiation (APBI) has been explored as a possible option to deliver adjuvant irradiation after lumpectomy in selected patients undergoing BCT (3). The primary advantage of APBI is the reduced treatment time and potentially reduced toxicities. Most phase I/II studies (and more recently, some phase III data) have demonstrated acceptable 5 and 10-year rates of local control and cosmesis using this treatment approach (4-6).

Studies using catheter based interstitial brachytherapy (IB) as the APBI technique have provided the largest group of patients with the longest follow-up to date. However, one of the primary disadvantages of IB to deliver APBI is the complexity and reproducibility of the procedure. Conventional IB is an invasive technique and consists of the placement of up to 20 needles or catheters around the site of the tumor removal (i.e., lumpectomy cavity). These needles or catheters are then temporarily loaded with a radiation source to deliver adjuvant irradiation (i.e., APBI) to the tissues surrounding the lumpectomy cavity in 4-5 days. When the radiation is completed, the needles or catheters are removed (7). Even using the best imaging/placement methods available, the technique is complex and requires a great deal of experience and skill to position the needles or catheters to cover the required treatment area (8). In addition, widespread patient acceptance of this method of APBI has not been demonstrated.

The MammoSite® applicator (Hologic Inc, Bedford, Massachusetts) was developed to address these concerns (9). The MammoSite® allows an easier implant and more reproducible radiation delivery to the target tissue area than IB. The MammoSite® has a nylon tube (for the radiation source to travel in) with a balloon attached at the end to expand and conform to the lumpectomy cavity. The MammoSite® applicator is inserted into the cavity created by the tumor removal surgery, either at the time of lumpectomy or shortly thereafter. The applicator is then inflated and expands to fill the cavity. The radiation can then be delivered using commercially available radioactive sources using the center nylon tube. This single central source creates a symmetrical radiation delivery from the inside of the cavity to the adjacent tissues surrounding the balloon where residual cancer is most likely to exist while potentially reducing damaging radiation delivery to the surrounding normal tissues.

In the first phase I/II clinical trial with the MammoSite® balloon catheter, 43 patients received radiation therapy as primary treatment (10). Patients experienced only mild to moderate side effects, including skin erythema (57%), dry desquamation (13%) and moist desquamation (5%) as acute toxicities that were related to the radiation therapy dose. The study demonstrated that the device was safe and well tolerated which resulted in FDA clearance on May 6, 2002. Five-year cosmetic results have been good to excellent in 83% of the women treated in this study and no local recurrences have been observed to date with a median follow-up of 66 months (11).

The safety and effectiveness of the MammoSite® Radiation Therapy System (RTS) as a replacement for whole breast irradiation in the treatment of early stage breast cancer is quickly being established. Multiple single-institution experiences have demonstrated acceptable early local control and cosmesis (with minimal toxicities) (12). The most recent data on the use of the MammoSite® to deliver APBI by the American Society of Breast Surgeons has shown a 3-year ipsilateral breast local recurrence (IBTR) rate of only 1.8% in the first 400 patients treated on this registry trial (median follow-up 36 months) and 93% of these patients were reported to have good/excellent cosmesis (13) (Verbal communication, Beitsch: American Society of Clinical Oncology, 2007).

One of the major limitations of the use of the MammoSite® to deliver APBI has been conformance of the surface of the balloon to the lumpectomy cavity and providing an acceptable skin spacing (14). Since the radiation dose is prescribed to 1.0 cm from the surface of the balloon, a separation of at least 7 mm (balloon surface-to-skin distance) is generally required to avoid excessive skin dose (and the potential for subsequent sub-optimal cosmesis). In addition, if conformance around the balloon is poor, breast tissue surrounding the lumpectomy cavity (e.g., the tissues at greatest risk for harboring residual disease) may be sub-optimally treated. As a result, there are significant limitations on the applicability of the use of the device in many patients.

With increased treatment experience with both interstitial brachytherapy and the MammoSite® balloon device, several dosimetric parameters have emerged and have been used as treatment planning goals to reduce potential toxicity and optimize target coverage. Many of the dosimetric parameters initially used to judge the appropriateness for treatment were based on the dosimetric performance of the MammoSite® device. The dosimetric ability of this device is dependent on the placement, the location within the breast, the symmetry of the balloon, and the fit within the cavity. Often, to reduce the number of aborted cases, the physician is forced to compromise on the dosimetric parameters and therefore risk toxicity. Rather than setting dosimetric goals at a level for optimal inclusion, parameters more importantly should be set to optimize target coverage and reduce toxicity.

In an effort to do this and for the purpose of this study, dosimetric parameters have been derived from treatment outcome experiences as well as appropriate application of brachytherapy principles (15, 16). These five dosimetric goals are comprised of: (1) dosimetric coverage of 95% of the target volume with 95% of the prescribed dose, (2) limiting the volume of breast tissue that receives 150% of the prescribed dose to less than 50 cc and (3) that which receives 200% of the dose to less than 10 cc, (4) assuring that the skin receives less than 125% (42.5 Gy) and (5) the rib less than 145% (50 Gy) of the prescribed dose. To determine in what percentage of MammoSite® treated patients all dosimetric goals were able to be met, the dosimetric information from 82 patients treated at the Virginia Commonwealth University between 2005 and present were reviewed (Verbal communication, Arthur: 2008). Allowing a 5% relaxation of dosimetric goal 1 above (i.e., dosimetric coverage of 95% of the target volume with 95% of the prescribed dose), the evaluation of this pilot data revealed that only 60% of the cases treated with the MammoSite® device met all of the above listed dosimetric criteria.

The Contura™ MLB (SenoRx, Inc., Aliso Viejo, California) was developed to address these critical issues. Through the use of four additional lumens that are off-set 5 mm from the single-central catheter lumen design (see **Appendix 2**), significant dose shaping is possible. This

results in the ability to reduce the skin dose and treatment restrictions (as a result of insufficient skin spacing). These modifications in the design of the balloon have the potential for greater utilization of balloon brachytherapy to deliver APBI. Preliminary dosimetric data on ten clinical cases planned using the Contura™ MLB have shown that there are geometric scenarios where loading of only a central lumen presents dosimetric limitations. The multi-lumen balloon (MLB) approach can lead to significant improvements in dose coverage of the partial breast target with simultaneous dose reductions to adjacent structures such as skin, chest wall, and pectoralis muscle. In effect, the Contura™ MLB may provide (1) increased utilization of balloon brachytherapy to deliver APBI by allowing the treatment of cases currently borderline or unacceptable for APBI, and (2) improved radiation delivery for standard patients currently managed with balloon brachytherapy (i.e., further improvement in normal tissue avoidance and/or more optimal coverage of the target).

The current study is designed to investigate the dosimetric capabilities, the clinical outcomes (local control, cosmesis, and toxicities) and the clinical scenarios of 342 patients treated with balloon brachytherapy using the Contura™ MLB to deliver APBI. Several institutions will be asked to participate in this study which will also evaluate the practical use of the device in the clinic and determine which scenarios where only the Contura™ MLB could be used to deliver APBI with balloon brachytherapy. Since the use of the Contura™ MLB allows significant improvements in balloon brachytherapy dosimetry through dose shaping, modifications in skin dose, radiation margin, implant homogeneity, chest wall dose and normal tissue exposure will be carefully monitored.

Sites participating in the study will be asked to provide clinical, dosimetric, and follow-up data. Patient eligibility criteria have been designed not to overlap with potential candidate patients for the NSABP 39/RTOG 0413 Phase III study. As such, only low risk patients will be allowed. Patients must be enrolled in the protocol prior to the initiation of brachytherapy (17). Sites will be required to undergo physics training in order to enroll patients. Stringent dosimetric guidelines are provided to ensure the lowest risk of acute and chronic toxicity. Sites will also be required to provide comprehensive data on the multiple dosimetric characteristics of the implant. Finally, careful follow-up will be required and will include comprehensive data on treatment efficacy and acute and chronic toxicity.

Patients who are selected for implantation of the Contura™ MLB are generally those who have early stage invasive breast cancer or DCIS. The Contura™ MLB may provide significant benefits over alternative methods. The new device is expected to provide a significantly better success rate over the historic single central lumen balloon's rate. Definition of success is defined in **Section III(A)**, and the sample size is justified against the rate of success by this definition. As part of a secondary analysis, disease control, cosmetic results, and toxicity rates will be evaluated and compared against historic outcomes. For patients that opt for lumpectomy followed by Contura™ MLB instead of conventional external beam radiation can reduce the length of treatment by up to five weeks. This therapy method may also reduce the exposure of normal tissue to damaging radiation, thus improving the quality of life of the patient and minimizing the potential damage of the radiation therapy.

II. STUDY DESIGN AND OBJECTIVES

A. Study Design

This multiple site, prospective, non-randomized study has been designed to compile information on the efficacy of the Contura™ MLB in delivering APBI in appropriately selected patients through evaluation of dosimetric success as compared with a single central lumen balloon device and through treatment outcomes.

Data collected during this study will include baseline patient demographics, information related to the time of implant, radiation therapy details, and removal of the device as well as recurrence data, cosmetic outcomes and toxicities. The patient's follow-up data will be collected during the patient's standard follow-up visits. The study will continue until 342 patients have been accrued and followed for five years.

B. Study Objectives

1. To compare the dosimetric efficacy of the Contura™ MLB with the historical efficacy rate of a single central lumen balloon device.
2. To quantify the dosimetric improvement of multi-lumen use over single lumen use through dosimetric comparison.
3. To estimate the local tumor control rate in the breast (and regional and distant sites) with the Contura™ MLB to deliver APBI.
4. To evaluate the cosmetic results in the breast utilizing the Contura™ MLB to deliver APBI.
5. To evaluate treatment related toxicities in the breast utilizing the Contura™ MLB to deliver APBI (i.e., seroma formation, infection, fat necrosis, pain, telangiectasia, and pigmentation).
6. To determine the frequency and type of clinical scenarios where only the Contura™ MLB could be safely used to deliver adjuvant APBI using balloon brachytherapy because of:
    a. skin spacing concerns,
    b. sub-optimal balloon conformance to the lumpectomy cavity,
    c. dosimetric limitations (i.e., radiation "hot spots" creating potential concerns such as fat necrosis or other late tissue toxicities),
    d. normal tissue concerns (i.e., proximity to chest wall, heart, etc.), or
    e. sub-optimal surgical margins requiring eccentric expansion of the full-dose radiation margin to cover any possible residual disease.

III. STUDY ENDPOINTS

A. Primary Endpoint

The primary objective of the study is to compare the success rate of the Contura™ MLB with a single central lumen balloon device. "Success" is defined as a combined criterion of meeting all the following criteria:

1. Maximum total skin dose $\leq$ 125% of prescribed dose (i.e., 42.5 Gy)
2. Maximum total rib dose $\leq$ 145 % of prescribed dose (i.e., 50 Gy)
3. V 150 $\leq$ 50 cc
4. V 200 $\leq$ 10 cc
5. 95% coverage of the target volume with $\geq$ 95% of the prescribed dose with 5% relaxation of this stated boundary

Pilot data from Virginia Commonwealth University with 82 patients show 60% success rate with a single central lumen balloon device according to the above definition (Verbal communication, Arthur: 2008).

B. Secondary Endpoints

The secondary endpoints of the treatment will be measured by disease control, cosmetic results and toxicity rates during a follow up period of 5 years, as well as by identifying the clinical scenarios where only the Contura™ MLB could be safely used to deliver adjuvant APBI using balloon brachytherapy.

IV. STUDY POPULATION

Three hundred and forty two patients capable of comprehending the nature of the study are to be entered into the study provided the patient conforms to the following criteria.

A. Inclusion Criteria

1. Able and willing to sign informed consent
2. Age 50 or older at diagnosis
3. Life expectancy greater than 10 years (excluding diagnosis of breast cancer). Co-morbid conditions should be taken into consideration.
4. Surgical treatment of the breast must have been lumpectomy. The margins of the resected specimen must be histologically free of tumor (negative surgical margins per NSABP criteria).
5. On histologic examination, the tumor must be DCIS and/or invasive breast carcinoma.

6. For patients with invasive breast cancer, an axillary staging procedure must be performed. Either:

   a. sentinel node biopsy (SNB) alone if sentinel node(s) is/are negative; or

   b. axillary dissection (minimum of six axillary nodes removed); and

   c. the axillary node(s) must be pathologically negative.

7. The T stage must be Tis, T1, or T2. If T2, the tumor must be ≤ 3.0 cm in maximum diameter.

8. Estrogen receptor positive tumor

B. Exclusion Criteria

1. Age < 50 at diagnosis (regardless of histology)

2. Pregnant or breast-feeding (if appropriate, patient must use birth control during the study)

3. Active collagen-vascular disease

4. Paget's disease of the breast

5. Prior history of DCIS or invasive breast cancer

6. Prior breast or thoracic RT for any condition

7. Multicentric carcinoma (DCIS or invasive)

8. Synchronous bilateral invasive or non-invasive breast cancer

9. Surgical margins that cannot be microscopically assessed or that are positive

10. Positive axillary node(s)

11. T stage of T2 with the tumor > 3 cm in maximum diameter or a T stage ≥ 3

12. Estrogen receptor negative tumor

V. STUDY SCHEDULE

A. Planned Examination Schedule

Patients will be examined and evaluated according to the following standard of care steps:

Step 1 Lumpectomy

Step 2 Contura™ MLB placement

Step 3 Treatment planning

Step 4 Brachytherapy treatments (10 fractions over 5 days)

Similarly, patients should be seen according to the standard of care for follow-up office visits. The first post-RT office visit should occur between 2-8 weeks post-treatment. Thereafter, ideally the visits will occur at least every 6 months through year 5.

B. Screening and Enrollment

Prior to enrollment in the study, potential participants will be evaluated to determine eligibility. The investigator will explain the study purpose, procedures, and patient responsibilities to the potential participant. The participant's willingness and ability to meet the follow up requirements will be evaluated. Written informed consent will be obtained from all potential study participants prior to participation.

At this time, patient demographics and a baseline mammogram will be documented.

C. Surgery and Applicator Placement

The patient will undergo standard lumpectomy surgery to remove the tumor. This surgery must provide negative surgical margins using the NSABP definition.

The Contura™ MLB should be placed in a separate procedure using ultrasound guidance after surgery. The balloon of the Contura™ MLB is inflated with a saline/contrast mixture (maximum of 2-3% contrast) to fill the cavity at the time of placement. The balloon will remain inflated throughout the duration of the radiation and will be removed after the last fraction. Post implant imaging (treatment planning CT scan) must be performed after insertion of the Contura™ MLB to evaluate the patient for skin spacing, symmetry and conformance of the applicator.

D. Treatment Planning

Standard treatment planning guidelines for APBI will be employed and CT imaging is mandatory for treatment planning. CT-based 3-D brachytherapy treatment planning will be conducted using commercially available software and equipment. The treatment will be performed using available high dose rate (HDR) brachytherapy. (Refer to **Section VI(C&D)** for specific details regarding dosimetric guidelines and quality assurance criteria.)

E. Brachytherapy Treatment

In general, brachytherapy should start between 1-5 days after balloon placement. The dose for primary therapy will be 34 Gy delivered to the PTV divided in 10 fractions over 5 days. The treatment fractions are delivered twice a day with at least six hours separating each fraction.

In addition, to confirm that the patient's position is identical to the position of the initial planning CT, the applicator's inflation status and rotational motion will be verified prior to each fraction. If any problems are found during the confirmation check, refer to the Instructions for Use (refer to **Appendix 3** or the applicator package for the most recent version). All treatments will be completed using a commercially available HDR and 192 Ir radioactive sources.

F. Applicator Removal

The applicator removal should be scheduled after completing the brachytherapy. The applicator should be removed using standard sterile technique and the applicator exit/entrance site should be dressed according to standard medical practice.

G. Post Applicator Removal Follow-Up Visits

The patient should be seen according to the standard of care for follow-up office visits. The first post-RT office visit should occur between 2-8 weeks post-treatment. Thereafter, ideally the visits will occur at least every 6 months through year 5 (see **Appendix 1**). Mammography should be performed according to institutional standards of practice and is generally performed as a baseline 6-12 months after brachytherapy and repeated annually.

The occurrence of adverse events, including toxicities, second primary cancers, and deaths (on therapy or prior to evidence of disease progression), will be monitored continuously. Recurrences and new cancers detected using standard imaging will be documented. Biopsy and additional treatment will also be documented, if applicable. Cosmetic grading, seroma formation, infection, fat necrosis, pain, telangiectasia, and pigmentation must be evaluated and reported at each visit.

H. Study Completion

An exit case report form must be completed for all study participants.

1. Patient Completion – A patient is considered to have completed the study if the follow-up examinations were completed through year 5.

2. Patient Discontinuation – A patient may be discontinued from the study at the discretion of the investigator if the patient's condition deteriorates or if the investigator decides that continuing in the study may be detrimental to the health or welfare of the patient.

3. Patient Lost to Follow-Up – A patient may be lost to follow-up for non-treatment related reasons. Reasons for loss to follow-up include, but are not limited to:

   a. voluntary withdrawal from the study by the patient (note: voluntary withdrawal may occur at any time during the study and will not affect future medical treatment or benefits)

   b. patient has moved from the area

   c. patient is unwilling or unable to return for follow-up

VI. CONTURA™ MLB

A. Device Description

1. Applicator and Tray

The Contura™ MLB applicator is used to position tissue and radioactive sources during breast brachytherapy treatments. It consists of a multi-lumen tube with an inflatable balloon assembly at its distal end. The Contura™ MLB is available with a variable diameter ranging from 4-5 cm. The balloon fill volumes are listed below:

Balloon Fill Volume (cc)	Balloon Diameter (mm)
33	40
35	41
37	42
39	43
42	44
44	45
47	46
50	47
52	48
55	49
58	50

The Contura™ MLB applicator tray is supplied in sterile packaging and comes packaged with the equipment needed to implant and inflate the applicator. The Instructions for Use and chart labels are also provided in the applicator tray. A Contura™ MLB balloon that will expand to a 5-6 cm diameter is in development and when available will be allowed for use to treat patients in this trial. Corresponding Instructions for Use will be provided in the applicator package.

2. Afterloader Connector Accessories

Standard adapters or transfer tubes needed to connect the Contura™ MLB applicator to the various commercially available HDR machines are available from the HDR manufacturers.

B. Physics Training

It is the responsibility of each participating institution to have a thorough understanding of the proper placement, management and removal of the Contura™ MLB prior to study participation and that proper and effective quality assurance procedures are followed for each case. The physics training process is an exercise for the participating institution to evaluate their site specific infrastructure and individual expertise prior to patient treatment initiation. After successful completion of this training exercise, SenoRx provides a certificate of completion.

C. Dosimetric Guidelines and Quality Assurance Criteria

Sites will be required to complete the physics training in order to enroll patients. Stringent dosimetric guidelines are provided to ensure the lowest possible risk of acute and chronic toxicity. Sites will also be required to provide data on multiple dosimetric characteristics of the implant.

1. Imaging (Planning & Quality Assurance)

A treatment planning CT scan with the patient in an easily reproducible position with the Contura™ MLB in place will be required for assessing appropriateness for treatment and treatment planning. The CT scan should at least include 3 cm both cephalad and caudal to the Contura™ MLB for proper assessment of dose delivery. A CT scan thickness of ≤ 0.3 cm should be employed. The following structures will be contoured: (a) balloon surface, (b) planning target volume for evaluation (PTV_EVAL) – (see below), (c) trapped air and/or fluid, (d) skin surface, and (d) aspect of the closest rib that is adjacent to the balloon. The target volumes and normal tissue structures should be outlined on all CT cuts when appropriate.

It is critically important that at the time of the planning CT, the rotational orientation of the Contura™ catheter is documented so that prior to each treatment the proper orientation can be reproduced. It is suggested that the shaft orientation line position be noted and a skin mark or the skin incision be used for consistent rotational positioning. Additionally, a single dummy marker wire can be placed into lumen #1 to document orientation of the device for proper CT planning.

2. Target Volumes

As the implanted balloon moves with the target, compensation for variability of treatment set-up and breathing motion is not needed; the planning target volume for evaluation (PTV_EVAL) = clinical target volume (CTV) = planning target volume (PTV). Therefore, within this protocol, only the PTV_EVAL will be referenced. The

PTV_EVAL will be delineated as the breast tissue volume bounded by the uniform expansion of the balloon radius in all dimensions by 10 mm less the balloon volume and will be limited to 5 mm from the skin surface and by the posterior breast tissue extent (chest wall and pectoralis muscles are not to be included).

When determining dose coverage of the PTV_EVAL to assure compliance with dose requirements, as outlined in **Section (VI)(D)**, the volume of trapped air/fluid must be accounted for as it displaces a percentage of the target beyond 1 cm from the balloon surface. The area of trapped air/fluid will be contoured at each level, a total volume obtained and the percentage of the PTV_EVAL that it displaces calculated. When determining the PTV_EVAL dose coverage, this displaced percentage must be subtracted. For example, if the percentage of PTV_EVAL displaced by trapped air/fluid is calculated to be 5%, then to comply with criteria, the dose coverage must be at least 100% of the PTV_EVAL receiving 95% of the prescribed dose. If the percentage of PTV_EVAL displaced by trapped air/fluid is greater than 10%, then it is not possible to achieve acceptable dose coverage.

3. Contura™ MLB Placement and Treatment Planning

The Contura™ MLB should be placed with a closed cavity placement technique. Radioactive source location, number of lumens, number of positions and dwell times are at the discretion of the physician and will be determined by High Dose Rate CT-based 3D treatment planning to produce the optimal conformal plan in accordance with volume definition and dose requirements. The treatment plan used for each patient will be based on analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV_EVAL and critical normal tissues.

4. Determination of Appropriateness for Treatment

Appropriateness for treatment will be based on the ability to achieve the dosimetric goals. However, three basic parameters can be used for determining whether the geometric placement of the Contura™ MLB will provide the ability to achieve the dosimetric goals. These basic parameters include: (a) tissue-balloon conformance, (b) balloon symmetry, and (c) minimal balloon surface-skin distance. As a result of the dose shaping capabilities of the Contura™ MLB, minimum requirements for these geometric parameters are case dependent. The general rules are outlined as follows:

a. Tissue-Balloon Conformance

Ideally, the lumpectomy cavity surface should be in direct contact with the entire balloon surface assuring maximum prescription dose coverage of the PTV_EVAL. Frequently air and/or fluid will be identified between the lumpectomy cavity and balloon surface. Either as a result of an irregular cavity shape or because the air/fluid is trapped, a less than ideal conformance results and "pushes" a percentage of the PTV_EVAL beyond the prescription isodose line coverage. To determine the significance of the trapped air/fluid, these volumes will be contoured and used in calculating PTV dose coverage (**Section (VI)(D)**). Typically, when the volume of trapped air/fluid is < 10% of the PTV, acceptable dose coverage can be achieved.

b. Balloon Symmetry

The symmetry of the balloon surface with respect to the central lumen can have, particularly for the single lumen balloon devices, negative effects on the dosimetric coverage of the PTV as well as on the volume of tissue receiving more than 200% of the prescribed dose. Balloon asymmetry, when existent, can be corrected with the dose shaping capabilities of the Contura™ MLB. The success and degree of correction will depend on the degree of asymmetry.

c. Minimal Balloon Surface-Skin Distance

Ideally, the minimal balloon surface-skin distance should be $\geq$ 7 mm. However, if the balloon-skin thickness is 3-7 mm, then it may be possible to employ offset lumens and reduce the max skin dose. The maximum acceptable skin dose for treatment is $\leq$ 145% of the prescription dose.

5. Dose Prescription and Delivery

Treatment utilizing the Contura™ MLB should begin within 1-5 days from the acquisition of the planning CT. High dose-rate brachytherapy treatment delivery will be employed, low dose-rate dose delivery will not be allowed. The balloon will remain inflated throughout the treatment course. A total of 34 Gy will be prescribed to the PTV_EVAL such that the dosimetric requirements in **Section VI(D)** are satisfied. Two fractions per day, each of 3.4 Gy, separated by at least six hours, given in five consecutive working days (i.e., weekends without treatment are allowed) will sum to 10 fractions and 34 Gy.

Prior to each treatment, it is necessary to assure:

a. Continued integrity of the balloon throughout treatment, as determined by ultrasound or x-ray performed prior to each delivered fraction and evaluated for any change in balloon diameter. These should be compared to a similar study performed at the time of treatment planning. If a change in balloon geometry is noted, this should be addressed prior to additional treatment.

b. The patient's position in which the planning CT was obtained is reproduced prior to each fraction.

c. To assure proper orientation of the device throughout treatment, the orientation line will be identified and the proper alignment, as compared to the alignment at the time of planning, will be verified and corrected if any rotational deviation is seen prior to each treatment.

D. Quality Assurance of Dose Distribution and Dosimetric Comparison

After target volumes have been delineated, each treatment plan shall be developed based on the dose distribution parameters listed below. In addition, for dosimetric comparison, for each case a plan will be generated for Contura™ MLB as well as single central lumen

single dwell and single central lumen multi-dwell. Each of the three plans will be optimized for PTV_EVAL coverage with respect to the dosimetric goals listed below. This data will serve to confirm findings of the VCU single central lumen balloon dosimetric pilot trial and provide direct dosimetric comparison for each individual patient to help elucidate clinical scenarios where multi-lumen use is beneficial (Verbal communication, Arthur: 2008).

1. Goal

    a. Dose volume histogram analysis of target coverage will confirm ≥ 95% of the prescribed dose covering ≥ 95% of the PTV_EVAL. The volume of trapped air/fluid will be accounted for using methodology described in **Section VI(C)(2)**.

    b. Maximum skin dose will be reduced to as low as achievable while satisfying all dose parameters but should not exceed 125%.

    c. Maximum rib dose will be reduced to as low as achievable while satisfying all dose parameters but should not exceed 145%.

    d. The volume of breast tissue receiving 150% (V150) of the dose should be reduced to as low as achievable while satisfying all dose parameters, but should not exceed 50 cc.

    e. The volume of breast tissue receiving 200% (V200) of the dose should be reduced to as low as achievable while satisfying all dose parameters, but should not exceed 10 cc.

2. Acceptable

    a. Dose volume histogram analysis of target coverage will confirm ≥ 90% of the prescribed dose covering ≥ 90% of the PTV_EVAL. The volume of trapped air/fluid will be accounted for using methodology described in **Section VI(C)(2)**.

    b. Maximum skin dose will be reduced to as low as achievable while satisfying all dose parameters but should not exceed 145%.

    c. Maximum rib dose is unrestricted.

    d. The volume of breast tissue receiving 150% (V150) of the dose should be reduced to as low as achievable while satisfying all dose parameters but should not exceed 50 cc.

    e. The volume of breast tissue receiving 200% (V200) of the dose should be reduced to as low as achievable while satisfying all dose parameters but should not exceed 10 cc.

3. Unacceptable

   a. Dose volume analysis of the target volume confirms < 90% of the prescribed dose and/or < 90% coverage of the PTV_EVAL The volume of tapped air/fluid will be accounted for using methodology described in **Section VI(C)(2)**.

   b. Maximum skin dose exceeds 145%

   c. Maximum rib dose is unrestricted

   d. The volume of breast tissue receiving 150% (V150) of the dose exceeds 50 cc

   e. The volume of breast tissue receiving 200% (V200) of the dose exceeds 10 cc

VII. DISEASE CONTROL

A secondary endpoint of the study is local tumor control at 5 years. This will be assessed by physical examination and mammography. All cases of local failure must be proven using pathologic criteria. Note: Investigators are also asked to report any contralateral, regional (classified as an axillary, supraclavicular, internal mammary node, or skin recurrence) or distant failure.

The location of the local ipsilateral failure in relation to the original cancer will be recorded. Criteria established by Recht et al will be used to help classify the type of local in-breast recurrence as follows (18):

True Recurrence/Marginal Miss Failure (TR/MM): A TR/MM failure is defined as a recurrence of the treated cancer within or immediately adjacent to the primary tumor site.

Elsewhere Failure (E): An 'E' failure is defined as local recurrence several centimeters from the primary site and is generally believed to be a new primary cancer.

VIII. COSMESIS

A secondary endpoint of the study is cosmetic results. This will be assessed by physical examination at each follow-up visit and categorized according to the four category Harvard Scale definitions as follows:

Excellent	The treated breast looks essentially the same as the opposite breast
Good	Minimal but identifiable effects of radiation on the treated breast
Fair	Significant effects of radiation on the treated breast
Poor	Severe normal tissue sequelae secondary to irradiation

IX. BREAST TOXICITIES

A secondary endpoint of the study is toxicity rates. This will be assessed by physical examination at each follow-up visit.

A. Seroma Formation

Investigators are asked to record information regarding seromas at each follow-up visit. Seromas are defined as transient, persistent, or symptomatic and will be monitored for (1) method of detection, (2) signs and symptoms, and (3) method of treatment.

B. Infection

Investigators are asked to record information regarding infections at each follow-up visit. Infection will be evaluated for (1) method of detection, (2) location, (3) signs and symptoms, and (4) method of treatment.

C. Fat Necrosis

Investigators are asked to record information regarding fat necrosis at each follow-up visit. Fat necrosis will be evaluated for (1) method of detection, (2) signs and symptoms, and (3) method of treatment.

D. Pain

Investigators are asked to record information regarding pain at each follow-up visit. Pain will be evaluated for (1) location, (2) degree and extent of pain, and (3) method of treatment.

E. Telangiecstasia

Patients will be evaluated for telangiectasia at each follow-up visit. Telangiectasia will be graded 1-4 (Grade: 1 = less than 9 cm^2, 2 = 9-36 cm^2, 3 = greater than 36 cm^2, and 4 = whole field).

F. Pigmentation

Patients will be evaluated for skin pigmentation at each follow-up visit. Pigmentation will be graded 1-4 (Grade: 1 = localized, 4 = generalized).

X. ETHICAL CONSIDERATIONS

A. Risks Associated with the Use of the Contura™ MLB System

1. Categories

   a. Surgery – Complications associated with the surgical implantation of this applicator are similar to any tumor removal surgery with the implant of a post-surgical drain. Possible complications include, but are not limited to:

infection, bleeding, loss or impairment of nerve function, swelling (edema), hematoma, fluid accumulation, wound effusions, wound breakdown, ecchymosis, and scarring.

b. Applicator Implantation – Complications arising from implantation of the applicator include, but are not limited to: infection, bleeding, loss or impairment of nerve function, swelling (edema), hematoma, fluid accumulation, applicator migration, and histotoxic reactions. Device deflation may occur after placement requiring the placement of a second replacement Contura™ MLB or alternative treatment.

c. Brachytherapy Delivery – Complications arising from the delivery of brachytherapy (radiation treatment) include, but are not limited to: infection, loss or impairment of nerve function, swelling (edema), scarring, skin effects including dry/moist desquamation, hyperpigmentation, telangiectasia and radiation induced necrosis.

d. Imaging Procedures – As part of the clinical study patients will undergo both x-ray and ultrasound procedures and are subject to the associated risks. The risks associated with these procedures are minimal to non-existent.

2. Minimization of Risks

Although the risks outlined in **Section X(A)(1)** may occur, the likelihood of serious events occurring is considered uncommon. The potential risks have been minimized by:

a. Performing complete validation testing of the Contura™ MLB; implementing appropriate quality measures into the production; and providing adequate directions for use in the labeling.

b. The radiation dose and dose rate prescribed within the protocol are within standard brachytherapy doses. This will minimize untoward radiation effects.

c. Physicians who receive the Contura™ MLB practice within an institution that has completed the required web based physics training and are experienced in the field of oncology, surgery, and radiation therapy, which will help to minimize the risk to the patients involved.

d. Guidelines for patient selection and evaluation are intended to prevent the inclusion of patients who might be prone to injury due to this study, or who are inappropriate candidates for other reasons.

B. Potential Patient Benefits

The potential benefits of this applicator and treatment are:

1. Decreased likelihood of tumor recurrence
2. Reduction in the amount of radiation delivered to normal breast and organ tissue
3. Elimination of delays in systemic/local therapy
4. Reduction of treatment time

C. Informed Consent

Written informed consent will be obtained from all potential study participants. The study will be explained to the prospective patient by the investigator or his designee. The nature of the device will be explained together with the potential hazards of the surgical procedure, including any possible adverse events. The patient and the investigator will sign and date the informed consent form. One copy of the informed consent form will be retained with the patient records and a copy will be provided to the patient. The draft informed consent form may be found in **Appendix 5.**

D. Institutional Review Boards

This protocol and an informed consent form will be approved initially and reviewed at least annually by an institutional review board (IRB) constituted according to regulatory and institutional requirements. The IRB granting the initial approval shall be responsible for continuing review and approval of this study including the informed consent form. A copy of the IRB's dated approval will be retained in the study files. The central IRB for this study will be Western IRB (WIRB).

XI. DATA HANDLING AND RECORD KEEPING

A. Source Documents

Adequate original records will be maintained for the study, including (but not limited to) patient medical and surgical records, data collection forms, exam printouts, signed informed consent forms, device use records, and adverse event reports. All original source documentation will remain at the investigational site.

ALL INVESTIGATIONAL SITES MUST PROVIDE ACTUAL COPIES OF:

The pathology report used to establish the diagnosis of breast cancer **AND** the radiation treatment summary report from the site.

NOTE: The patient's name and any other individually identifiable information will be removed and replaced with the patient's study identification number.

B. Case Report Form Completion

Case Report Forms (CRFs) will be provided by SenoRx for each patient enrolled in the study. The draft CRFs may be found in **Appendix 6**. The appropriate CRF will be completed after each study examination. For paper CRFs, all CRFs will be completed in a legible manner in ink. (NOTE: Any corrections will be made by drawing a single line through the incorrect entry, entering the correct information, initialing and dating the change.)

All clinical data generated in the study will be submitted to SenoRx for quality assurance review, data entry and statistical analysis. All forms will be reviewed for completeness and evident recording errors. Questions or queries will be resolved by contact with the clinical sites. (NOTE: self evident changes may be made by SenoRx with notification to the site of the change made.)

C. Monitoring Oversight

SenoRx representatives will monitor this study in a manner consistent with any applicable health authority regulations and the clinical research standards adopted by SenoRx. The investigator will permit SenoRx representatives direct access to source data/documentation for study-related monitoring, audits, review and inspection.

D. Reports

The investigator will submit progress reports at least once yearly and at the completion of the study to the IRB. The investigator will also submit any additional reports as requested by the IRB as a condition of study approval (e.g., safety reports, etc.).

Throughout the accrual and active treatment periods of the trial, progress reports will be prepared and presented to the DSMB as necessary but minimally at 6-month intervals. These reports will include an assessment of toxicities, second primary cancers and on-therapy deaths. For serious and/or unanticipated adverse events, the decision to continue the registry study will be evaluated by the DSMB as appropriate (refer to **Appendix 4** for adverse event reporting criteria). After accrual is closed, adverse events and other information will be presented to the DMSB together with interim analysis results. Interim analysis will be performed annually once half of the patients have been enrolled.

E. Records Retention

The investigator will maintain accurate, complete and current study records during the clinical study.

XII. STATISTICAL CONSIDERATIONS

A. Patient Accrual

Successful IRB review/approval and physics training at the investigational sites is estimated to be complete in 6 months. The estimated accrual during the IRB/physics training period will slowly increase to an average of 30 patients per month. The total accrual to this trial is 342 patients. The projected time to reach this accrual goal is 18 months.

B. Statistical Analysis

Patient demographics, disease characteristics, treatment parameters and accountability of patients over time will be summarized descriptively by overall, invasive and DCIS patient populations. For continuous variables/measurements calculations of the mean, median, standard deviation and range of values will be performed. For categorical variables, number and percent of patients within each category will be calculated.

The primary hypothesis of the trial is that the rate of success with the Contura™ MLB is significantly different from the historic rate of success with the single central lumen balloon device. Here the definition of success is as defined in **Section III(A).** Historic data on the single central lumen balloon device shows a 60% success rate (Verbal communication, Arthur: 2008). A two sided Fisher exact test for the proportion of success with the Contura™ MLB being 70% will require 342 patients for 96% power at 5% level of significance. Alternative success criterion would have more strict condition on each of the variables, and is likely to show even larger deviation of the performance of the Contura™ MLB from the single central lumen balloon device.

The number and percent of patients who died, and with local failure, regional failure, or distant disease will be presented. Non-parametric estimates of the survival or recurrence free distributions or recurrence (failure) distribution will be obtained via life table methods. Associations between clinical, pathologic, and treatment-related variables and recurrence or survival event rates will be explored.

Cosmesis will be evaluated by determining the number and percent of patients within each response category (Excellent, Good, Fair, Poor) at yearly intervals. Additionally, calculating the distribution of responses after collapsing into Excellent/Good versus Fair/Poor categories will be performed. Associations between dichotomous cosmetic outcomes (Excellent/Good versus Fair/Poor) and treatment related variables will be explored.

The patient incidence of toxicities will be calculated. Associations between cosmesis and certain toxicities will be explored.

Disease control, cosmetic results, and toxicity rates will be presented by the entire study population, and by invasive and DCIS patient groups.

XIII. SELECTED DEFINITIONS

Brachytherapy	Using sealed or unsealed sources for a therapeutic dose of local radiation.
Breast Conserving Surgery	Surgery where cancer is removed, together with a margin of normal breast tissue. The whole breast is not removed.
cGy	Centigray, a measure of radiation dose delivered to tissue (1 cGy = 1 rad).
Cosmesis	The appearance of the breast following treatment
Dosimetry	Measurement of radiation doses
Fraction	Radiotherapy is usually given over several weeks. The dose delivered each day is known as a fraction.
Gray or Gy	In the SI system, the unit of absorbed radiation dose
HDR	High dose-rate brachytherapy – dose rates greater than 100 cGy per hour
Margin Status (NSABP)	Positive: Tumor in contact with inked margin Negative: Tumor not microscopically in contact with the inked margin Close: Tumor within 2 mm from the inked margin
Postmenopausal	Patient must meet one of the following criteria: • A prior documented bilateral oophorectomy, or • A history of at least 12 months without spontaneous menstrual bleeding, or • Age 55 or older with a prior hysterectomy, or • Age 54 or younger with a prior hysterectomy without oophorectomy (or in whom the status is unknown), with a documented FSH level demonstrating confirmatory elevation in the lab's post-menopausal range. Patients failing to meet one of these criteria will be classified as pre-menopausal.

XIV. REFERENCE LIST

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3. Arthur DW, Vicini FA: Accelerated partial breast irradiation as a part of breast conservation therapy. J Clin Oncol 23:1726-1735, 2005

4. Vicini FA, Antonucci JV, Wallace M, et al.: Long-term efficacy and patterns of failure after accelerated partial breast irradiation: a molecular assay-based clonality evaluation. Int J Radiat Oncol Biol Phys 68:341-346, 2007

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Surgeons MammoSite breast brachytherapy trial. Cancer 104:1138-1148, 2005

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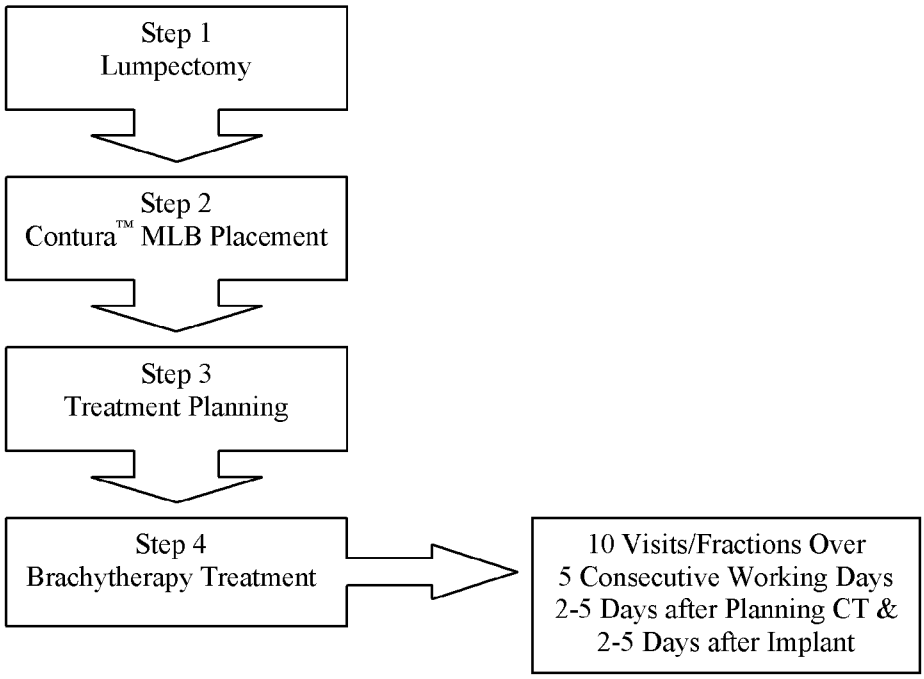
18. Recht A, Silver B, Schnitt S, et al.: Breast relapse following primary radiation therapy for early breast cancer. I. Classification, frequency and salvage. Int J Radiat Oncol Biol Phys 11:1271-1276, 1985

APPENDIX 1 – CONTURA™ MLB TREATMENT FLOW CHART & EXAM SCHEDULE

Contura™ MLB Treatment Flow Chart

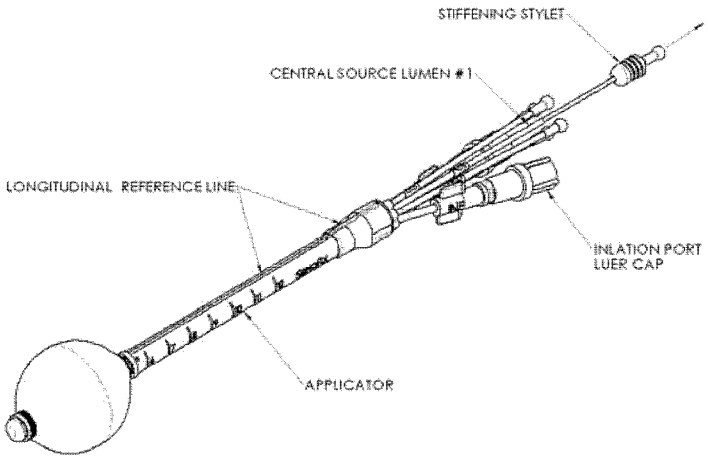


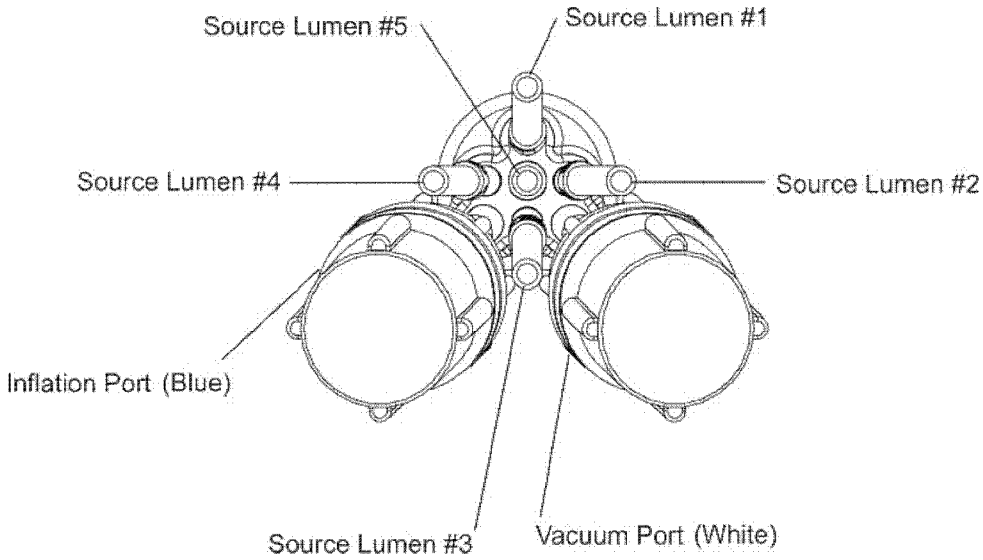
Exam Schedule

	Pre-RT Treatment	RT Treatment	Post-RT Treatment		
			2-8 Weeks	Every 6 Months	Annually
Demographics	X				
Breast Exam	X		X	X	
Breast Cancer Findings	X				
Contura™ MLB Placement		X			
Treatment Planning		X			
Brachytherapy Treatment		X			
MLB Removal		X			
Disease Status Evaluation			X	X	
Cosmesis Evaluation			X	X	
Toxicity Evaluations			X	X	
Mammogram/ MRI[1]	X[2]				X[3]

[1] MRI optional
[2] The pre-brachytherapy mammogram should be performed within 6 months of definitive surgery.
[3] Mammography should be performed according to institutional standards of practice and generally performed as a baseline 6-12 months after brachytherapy and repeated annually.

APPENDIX 2 – DEVICE DIAGRAM





APPENDIX 3 – INSTRUCTIONS FOR USE

DESCRIPTION

The Contura™ MLB Applicator consists of a multi-lumen catheter attached to an inflatable spherical balloon (Figure 1). Lumens are provided for attachment to commercially available HDR (High Dose Rate) remote afterloader equipment for passage of the radiation source delivery wire. Five radiation source wire lumens are provided, one central lumen located along the long axis of the Applicator and four curved lumens symmetrically offset from the central lumen. A removable stiffening stylet is positioned in the central lumen. Two proximal ports are also provided with Luer-type connectors for balloon inflation/deflation and for application of intracavitary vacuum.

The Contura™ MLB accessories provided for introduction and deployment include: trocar with split sheath, drainage catheter, three, 30 ml and one, 10 ml inflation syringes, #11 scalpel, contrast media tray, radiation lumen caps and labels (Figure 2).

Afterloader compatibility:
Model B001-45 - VariSource 200, VariSource iD and Nucletron HDR afterloaders
Model B011-45 - GammaMedPhis afterloader (Cannot be used with GammaMed 12i)

Warning: The safety and effectiveness of the SenoRx Applicator as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

INDICATIONS FOR USE

The Contura™ MLB Applicator is intended to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

CONTRAINDICATIONS

- The Applicator is not intended for use in cavities that are too small, too large and/or of shapes unable to conform to an approximately spherical, 4 to 5 cm diameter SenoRx balloon.
- The Applicator is not intended for use in patients with unusual anatomy including a highly curved rib structure and/or unequal amounts of tissue surrounding the cavity that may cause the SenoRx balloon to be asymmetrical.

WARNINGS

- Use caution when positioning the trocar tip near the chest wall or skin margin to avoid unintended tissue damage.
- Do not fill the Applicator with more than 38 ml of fluid as overfilling may result in balloon rupture and/or device failure.
- The Applicator must be pre-tested before implantation. Do not use the balloon if it is not approximately spherical and/or any leakage is detected.
- The breast cavity must be imaged before implantation to insure the Applicator will fit appropriately. Do not use if the cavity is too small or if a skin surface to balloon surface distance of less than 5 mm will result.
- To insure appropriate treatment dose distribution, the Applicator must be imaged prior to delivering each fraction of radiation to confirm correct position, balloon volume, skin spacing and conformance.
- If excessive resistance is encountered when attempting to remove the Applicator from the patient, surgical removal is recommended.

- Contrast media concentrations of less than 10% are recommended to prevent dose attenuation.
- Non-ionic contrast media is recommended for patients who are allergic to iodine-based agents.

PRECAUTIONS

- The Applicator must be used only by physicians trained in catheter implantation, radiation treatment planning and delivery.
- Metal vascular and marking clips should not be used during the lumpectomy procedure to prevent potential abrasion or puncture of the Contura™ balloon. Care should also be taken to direct suture knots and tails away from the cavity and whenever possible position tissue between the potential balloon surface and the tails.
- Store the SenoRx Applicator at room temperature (20 to 25°C).
- Care must be taken when handling and manipulating the Contura™ balloon to prevent damage and foreign material contamination of the balloon surface.
- A scalpel should be used to incise the skin prior to inserting the trocar tip.
- Do not inject fluids into the Vacuum Port.
- Replace Luer caps and radiation lumen caps after use.
- Only clinical personnel trained in the operation of HDR afterloaders should deliver radiation using the Applicator.
- Verify that the appropriate afterloader connectors are available and function with the Applicator prior to treatment.
- Be sure that the Applicator is as straight as possible and free of sharp bends and kinks prior to connecting to the HDR afterloader.
- Inspect package before use. Discard if seal is compromised or packaging is damaged.

COMPLICATIONS

Complications that may be associated with the use of the Contura™ MLB Applicator are the same as those associated with the use of similar devices. These may include: erythema, catheter site drainage, breast pain, ecchymosis, breast fibrosis, telangiectasia, breast induration, breast seroma, breast edema, dry desquamation, dry skin, skin discoloration, parasthesia, axillary pain, fatigue, pruritis, breast retraction, nausea, skin irritation, moist desquamation, hematoma, rash, asymptomatic fat necrosis, breast infection, breast blister and lymphedema.

HOW SUPPLIED

The Contura™ MLB Applicator and accessories are provided sterile and are intended for single patient use only.

DIRECTIONS FOR USE

- PLACEMENT - Refer to Figures 1 & 2

1. Use ultrasound to identify the lumpectomy cavity.
2. Open the Contura™ MLB Applicator sterile package and remove the Applicator (A) and one 30 ml Syringe (B). Remove the Inflation Port Luer Cap (C) and inject 5± ml of sterile saline into the Applicator and inspect for leaks and spherical symmetry. Discard Applicator if defective. Holding the Applicator by the connectors, with the balloon hanging vertically, completely withdraw the saline from balloon.
3. Prepare a maximum 5% contrast media/sterile saline solution in the Tray (D) provided.
4. Determine the desired point on the breast surface for the insertion of the Applicator. Inject appropriate anesthetic to the skin and pathway to the lumpectomy cavity. Make a skin incision with the scalpel at the insertion point of sufficient length to fully insert the Trocar (F) tip. Dilate the skin incision, if desired. Advance the Trocar with Split Sheath (G) into the cavity. Remove the Trocar.
5. Attach a 30 ml syringe to the Drainage Catheter (H) and drain any fluids within the cavity by inserting the Drainage Catheter through the Split Sheath and suctioning. Remove the Drainage Catheter.
6. Insert the Applicator through the Split Sheath into the cavity. Remove the Sheath.
7. Align the Radiopaque Line (I) on the catheter shaft with the skin incision.
8. Remove the stiffening Stylet (J) from the Central Source Lumen (K). Attach a red radiation source lumen Cap (L).
9. Using the syringes provided, inflate the Applicator balloon with the contrast media solution to the desired fill volume. Purge any air from the fill syringes before attaching them to the Applicator.

Desired balloon diameter	Approximate balloon fill volume
4 cm	33 ml
5 cm	58 ml

10. Replace the Luer Cap on to the Inflation Port (M).
11. Use ultrasound to confirm appropriate placement, volume and cavity conformance. Fluid and air surrounding the Applicator balloon may be aspirated with a 30 ml Syringe attached to the white Vacuum Port (N). The volume of the balloon may be adjusted through the blue Inflation Port (M). Replace Luer Caps when finished.
12. Confirm that the radiopaque line is aligned with the skin incision.
13. Apply a surgical dressing to the exit site with the catheter positioned to minimize bending.
14. Record the final balloon fill volume on the Labels provided and attach to the patient's chart.

- RADIATION DELIVERY - Refer to Figure 3

1. CT imaging should be used in conjunction with commercially available treatment planning software to determine the appropriate source lumens, source dwell positions and dwell times for optimized radiation delivery of a prescribed dose to the targeted treatment volume.
2. Note the orientation of the Contura™ MLB Applicator with respect to the radiopaque line on the catheter shaft. Verify correct Applicator orientation, balloon position, balloon volume, skin spacing and conformance using imaging prior to delivery of each fraction of radiation. Adjust if necessary.
3. The Applicator red-capped, radiation source wire lumens are numbered '1', '2', '3', '4' and '5' and positioned as shown in Figure 3. Lumen number '1' corresponds to the offset lumen closest and parallel to the longitudinal radiopaque line (M) along the outside of the catheter. Lumen number '5' corresponds to the central lumen. Remove the red caps and use commercially available connectors to attach the source lumens to the afterloader.

Note: When using the GammaMedPlus Afterloader, the radiation source lumens of the B011-45 Applicator must first be trimmed to length using the GammaMed length cutting gauge.

4. After each treatment replace the red caps.

- REMOVAL

1. Remove the Contura™ MLB Applicator by first attaching a syringe to the blue Inflation Port and deflating the balloon.
   Note: If difficulty is encountered deflating balloon with syringe:
   1) Reattach syringe and securely rotate clockwise to completely activate the valve. If the balloon still does not deflate, then
   2) Cut the blue Inflation Port tubing. The saline/contrast contents of the balloon will now drain from the end of the cut tubing.
2. Rotate and withdraw (unscrew) the Applicator from the cavity.

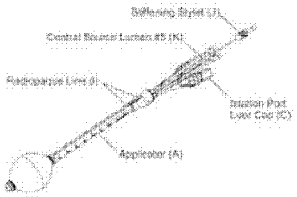


Figure 1: SENORX APPLICATOR

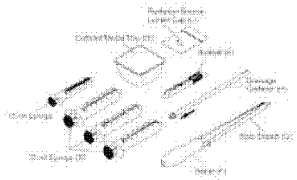


Figure 2: ACCESSORIES

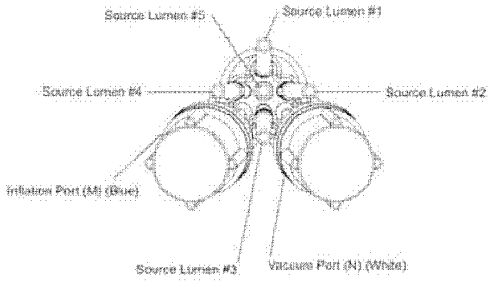


Figure 3: SOURCE WIRE LUMEN ORIENTATION

EXPLANATION OF SYMBOLS ON THE PACKAGE

REF	Catalogue Number
	Use by Date
LOT	Lot Number
CONT	Contents
STERILE R	Sterile (Gamma radiation)
	Attention, See Instructions for Use
2	Do Not Reuse
	Upper Temperature Limit
	Keep away from sunlight
	Keep dry

SenoRx Inc.
Aliso Viejo, California
USA

Contura™ Multi-Lumen Balloon - MLB

MULTI-LUMEN BALLOON SOURCE APPLICATOR FOR BRACHYTHERAPY

INSTRUCTIONS FOR USE

MODELS

B001-45
B011-45

Caution: **Federal (USA) law restricts this device to sale by or on the order of a physician.**

SENORX

B-0003 Rev. B
November 2007/ECO 1022

APPENDIX 4 – ADVERSE EVENT REPORTING

The investigator should report all serious adverse events that occur during the study.

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

All unanticipated adverse device effects are to be reported to SenoRx within 24 hours of learning of the adverse event.

Examples of anticipated events include: necrosis, infection, non-wound healing, dry/moist desquamation, bleeding, pneumothorax, poor cosmesis, seroma/hematoma, rib fracture, wound dehiscence, loss or impairment of nerve function, edema, histotoxic reaction, hyperpigmentation, telangiectasia, mild to moderate pain, severe pain (not resolving within the first month and requiring narcotics), ecchymosis, scarring, fibrosis, erythema, fever, skin burns, and superficial vein thrombosis). Refer to the "Instructions for Use" in **Appendix 3** for additional complications.

Serious Adverse Event (SAE)

A serious adverse event is defined as follows:

1) Death or threat to life;

2) Permanent impairment of a body function or permanent damage to a body structure; or

3) Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

All serious adverse events are to be reported to SenoRx within 5 days of learning of the adverse event.

Examples of serious events include: necrosis, non-wound healing, moist desquamation (that does not resolve within 4 weeks), unresolved bleeding, infection requiring medical or surgical intervention, pneumothorax, seroma/hematoma (symptomatic and/or cosmetically deforming), rib fracture, severe pain (not resolving within the first month and requiring narcotics) and wound dehiscence.

Events not considered serious include: erythema, infection (or suspected infections, i.e., fever) treated only with antibiotics, and seroma/hematoma (asymptomatic and/or not deforming).

Exhibit 18

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Attorneys for Defendants
CYTYC CORPORATION and
CYTYC SURGICAL PRODUCTS II, INC

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

XOFT, INC.,

Plaintiff,

vs.

CYTYC CORPORATION and PROXIMA THERAPEUTICS, INC.,

Defendants.

AND RELATED COUNTERCLAIMS.

Case No. CV 05-05312 RMW

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF CYTYC'S OPPOSITION TO XOFT, INC.'S MOTION TO COMPEL A FURTHER DEPOSITION OF JAMES STUBBS AND, TO PRODUCE DOCUMENTS WITHOUT OBJECTION

This opposition to Xoft's motion to compel a further deposition of Dr. James Stubbs and to produce documents without objections is based upon the accompanying Memorandum of Points and Authorities, the Declaration of Henry C. Su In Support of Cytyc's Opposition to Xoft's Motion to Compel a Further Deposition of James Stubbs and To Produce Documents Without Objection filed herewith, all papers and pleadings filed herein, and upon any other oral and documentary evidence that may be presented to the Court.

MEMORANDUM OF POINTS AND AUTHORITIES

I. INTRODUCTION

Xoft Inc.'s ("Xoft's" or "plaintiff's") two-part motion (1) to haul Dr. Stubbs back in for another deposition and (2) to set aside Cytyc's objections to Xoft's first set of Requests for Production of Documents so as to acquire privileged and non-responsive Cytyc documents (the "Motion") fails on legal and factual grounds. Xoft has suffered no prejudice from the short extension of time before receiving Cytyc's written objections to its Requests for Production. Cytyc's two-business day delay in responding to Xoft's first set of discovery requests is *de minimis* and has had no effect on the case whatsoever. Conversely, Cytyc would suffer a disproportionate harm if it has to disclose confidential, privileged and/or irrelevant information to its competitor Xoft. Moreover, Xoft's suggestion that Cytyc has engaged in discovery misconduct is unsupportable – Cytyc has diligently conducted its production of both documents and witnesses and Xoft's own conduct with respect to its own discovery obligations belies it suggestion. Cytyc therefore asks this Court to refuse Xoft the relief of unbounded access to Cytyc's information.

II. ARGUMENT

A. XOFT IS NOT ENTITLED TO A SECOND DEPOSITION OF DR. STUBBS.

1. Dr. Stubbs Already Testified Substantively For Almost 6.5 Hours.

Xoft's motion is nothing more than a plea for a "do-over" of Dr. Stubbs' deposition. Xoft neglects to mention in its Motion that Dr. Stubbs testified on substantive matters for 6 hours and 20 minutes on February 9, 2007 – nearly the full 7-hour time period presumptively authorized by Rules 30 and 45. *See* Fed. R. Civ. P. 30 & 45. Nor does Xoft mention that Cytyc did, in fact, offer to bring Dr.

Exhibit 19

FORM 10-K

HOLOGIC INC - HOLX

Filed: November 27, 2007 (period: September 29, 2007)

Annual report which provides a comprehensive overview of the company for the past year

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended: September 29, 2007

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission File Number: 0-18281

Hologic, Inc.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**04-2902449**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**

35 Crosby Drive, Bedford, Massachusetts 01730
(Address of Principal Executive Offices) (Zip Code)

Registrant's Telephone Number, Including Area Code (781) 999-7300

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on which Registered
Common Stock, $.01 par value	**Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: Rights to Purchase Preferred Stock

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by checkmark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer ☒ Accelerated Filer ☐ Non-Accelerated Filer ☐

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2). Yes ☐ No ☒

The aggregate market value of the registrant's Common Stock held by non-affiliates of the registrant as of March 30, 2007 was $3,079,547,382 based on the price of the last reported sale on the Nasdaq National Market on that date.

As of November 20, 2007 there were 125,341,631 shares of the registrant's Common Stock, $.01 par value, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement for the registrant's annual meeting of stockholders to be filed within 120 days of the end of its fiscal year ended September 29, 2007 are incorporated into Part III (Items 10, 11, 12, 13 and 14) of this Annual Report on Form 10-K where indicated.

Competition

The healthcare industry in general, and the markets our products compete in are highly competitive and characterized by continual change and improvement in technology, and multiple technologies that have been or are under development. A number of companies have developed, or are expected to develop products that compete or will compete with our products. Many of these competitors offer a range of products in areas other than those in which we compete, which may make such competitors more attractive to hospitals, radiology clients, group purchasing organizations, laboratories, physicians and other potential customers. In addition, many of our competitors and potential competitors are larger and have greater financial resources than we do and offer a range of products broader than our products. Some of the companies with whom we compete have or may have more extensive research, marketing and manufacturing capabilities and significantly greater technical and personnel resources than we do, and may be better positioned to continue to improve their technology in order to compete in an evolving industry. The companies that have significantly greater resources and product breadth than we do include General Electric Medical Systems (GE), Siemens, Philips, Fuji, Carestream Health (formerly Kodak), Becton, Dickinson and Company, Johnson & Johnson, Boston Scientific and Toshiba. Competitors may develop superior products or products of similar quality for sale at the same or lower prices. Moreover, our products could be rendered obsolete by new industry standards or changing technology. We cannot assure that we will be able to compete successfully with existing or new competitors.

Our mammography and related products and subsystems compete on a worldwide basis with products offered by a number of competitors, including GE, Siemens, Philips, PlanMed, Agfa, Carestream Health, Fuji, IMS Giotto, Sectra and Toshiba. Our FDA approved Selenia full field digital mammography system competes with products such as GE's and Siemens' full field digital mammography system. Siemens has adopted our DirectRay direct-to-digital detectors for use in their digital mammography system. In 2006, Fuji received FDA clearance to market its Computed Radiography (CR) mammography system, a lower priced alternative to digital mammography. CR requires the use of an analog or film based mammography system, where instead of film, a phosphor plate is used to capture a facsimile of the image. It then requires an extra step of having the plate processed on a specialized reader to create a digital image. In addition, Carestream Health has filed with the FDA to have its CR mammography product cleared for use. Agfa, Carestream Health, Cedara and Sectra have introduced approved mammography workstations and are marketing these in competition with our line of radiologist review stations. Other companies are marketing digital mammography systems or technologies in Europe and other international markets and have or are expected to apply for FDA clearance in the U.S. In addition, the FDA is considering reclassifying full field digital mammography systems from Class III to Class II devices. If this reclassification is implemented, these systems will be cleared for commercialization through the 510(k) process rather than the more rigorous pre-market approval process, which may increase the number of competitors entering the United States market. The Company anticipates that competition in the digital mammography market will intensify. While we offer a broad product line of breast imaging products, we compete most effectively in the high-end segment of the mammography market. We believe that our continued success will depend upon the continued success of our Selenia full field digital mammography system, as well as our ability to maintain our technology leadership through product enhancements and the development of new products and technologies. Although Selenia systems are priced higher than competing technologies, we believe the Selenia system provides outstanding performance in aiding physicians in the early detection of breast cancer due to its image quality and workflow features and functionality. Our MultiCare breast biopsy guidance systems compete with products offered by GE, Siemens, PlanMed, IMS Giotto and with conventional surgical biopsy procedures. We believe Siemens has entered this market with its newly acquired prone technology. We believe that competition for our mammography and related systems is based largely on image quality, product features, ease of use, product reliability and reputation as well as price and quality of service.

The primary competitor for our Suros biopsy and tissue extraction product line is Ethicon, a Johnson & Johnson company. There are many companies in the biopsy device market, but other principal competitors would include SenoRx and Bard. In addition, emerging companies like Sanarus, Rubicor and Intact Medical all share some smaller portion of the biopsy device market. We believe that competition for our biopsy and tissue

extraction product line is based largely on tissue sampling quality, product features, ease of use, product reliability and price.

The primary competitor for our CAD product line is iCAD, Inc. Although Carestream has introduced a CAD product, its acceptance has been limited. We believe that competition for our CAD product line is based largely on performance measurements of sensitivity and specificity, product features, ease of use and price.

International clinical guidelines recognize spine and hip bone density measurements as the standard for diagnosis of osteoporosis. GE is our primary competitor in the osteoporosis assessment market with bone density of the hip and spine systems. Other companies have developed lower priced x-ray and ultrasound based systems that assess bone status of peripheral skeletal sites, such as the heel, hand or wrist. Measurements of bone density at peripheral sites are utilized for screening for osteoporosis risk, and patients identified as at risk by peripheral testing are commonly referred for spine and hip bone density testing. We believe that competition in the field of osteoporosis assessment bone densitometry systems is based upon product versatility and features, price, precision, speed of measurement, reputation, cost and ease of operation, product reliability and quality of service. While we are generally not the lowest cost provider of dual-energy x-ray systems, we believe that we have been able to compete effectively because of our advanced technology and product features, including vertebral assessment imaging. We offer our Explorer system for the more price sensitive segment of the x-ray based osteoporosis assessment market, and our Sahara ultrasound bone analyzer for screening applications. We believe that competition in the field of osteoporosis assessment ultrasound systems is based on price, precision, speed of measurement, cost and ease of operation, reputation, product reliability and quality of service. Because ultrasound systems can only measure peripheral skeletal sites and do not have the precision of dual-energy x-ray systems, we believe dual-energy x-ray systems will continue to be the predominant means of diagnosis and monitoring of bone density changes for patients being treated for osteoporosis.

Our mini C-arm products compete directly with mini C-arms manufactured and sold by a limited number of companies including GE. We also compete with manufacturers of conventional C-arm image intensifiers including Philips, Siemens and GE. We believe that competition for our mini C-arm systems is based largely on price, quality, reputation, service and production capabilities. We believe that advantages of our mini C-arm systems include low levels of radiation, image quality or resolution, low product life cycle costs, mobility, quality and durability.

While Cytyc is the market leader in the sale of liquid-based slide preparation systems in the United States, it faces direct competition in the United States from Becton, Dickinson and Company ("Becton Dickinson"), who acquired TriPath Imaging, Inc. in the fourth quarter of 2006 and who also manufactures liquid-based slide preparation systems and slide imaging systems, and from other sample preparation systems in international markets. In addition, Cytyc competes with MonoGen, Inc. who uses a liquid-based slide preparation system. Cytyc also competes with the conventional Pap smear and other alternative methods for detecting cervical cancer and/or its precursors, such as that manufactured by Digene. Cytyc's products compete on the basis of a number of factors, including clinical performance, product quality, marketing and sales capabilities, manufacturing efficiency, price and customer service and support. Internationally, Cytyc's Thin Prep product competes with a variety of companies and other "off-market" (non-FDA-approved) tests, since fewer regulatory barriers exist in Europe as compared to the United States.

Cytyc is currently the only provider of a FullTerm Fetal Fibronectin Test for predicting the risk of preterm birth. However, this product could experience competition for the preterm birth diagnostic products from companies that manufacture and market pregnancy-related diagnostic products and services. In addition, healthcare providers use diagnostic techniques such as clinical examination and ultrasound to diagnose the likelihood of preterm birth. Healthcare providers may choose to continue using these techniques to assess their patients, rather than use the FullTerm Fetal Fibronectin Test. They may also choose to use these techniques in conjunction with our FullTerm Test to predict preterm birth.

Cytyc's NovaSure System currently faces direct competition from Johnson & Johnson, Boston Scientific Corporation, American Medical Systems, Inc. and Microsulis Medical Limited, each of which currently markets

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an FDA-approved "second generation" endometrial ablation device for the treatment of excessive menstrual bleeding. In addition to these devices, there exist alternative treatments to Cytyc's NovaSure System, such as drug therapy, hysterectomy, dilation and curettage and rollerball ablation. Rollerball ablation and the Johnson & Johnson endometrial ablation device have been in use for a longer time than Cytyc's procedure for the treatment of excessive menstrual bleeding. Internationally, Cytyc's products compete with drug therapy, as well as other endometrial ablation devices, including Johnson & Johnson's Thermachoice, Boston Scientific Corporation's HTA, the Microsulis Endometrial Ablation device and two other relatively small companies that market products that are not FDA approved. Because drug therapy is an alternative to Cytyc's NovaSure procedure, competitors to this product also include many major pharmaceutical companies that manufacture hormonal drugs for women.

As a result of the relatively short period of time Cytyc's MammoSite and GliaSite Systems have been in the market, these products face competition from the more commonly-known alternatives, such as treatment using external beam radiation, which has longer-term data on patient outcome, and future products such as Xoft Microtube, Inc.'s ("Xoft") electronic brachytherapy, SenoRx's Contura and Cianna Medical's SAVI. Internationally, Cytyc's MammoSite product faces competition from traditional mastectomy, whole breast radiation therapy after lumpectomy, and a more radical breast-conserving procedure called a quadrantectomy. Additional radiation therapy methods, such as intraoperative radiation therapy, are being explored in Europe by potential competitors; however, such alternative methods have not achieved widespread commercial use.

Manufacturing

We have historically purchased many of the components and raw materials used in our products from numerous suppliers worldwide. In some cases, we have established long-term supply contracts with our suppliers. For reasons of quality assurance, sole source availability or cost effectiveness, certain components and raw materials used in the manufacture of our products are available only from a sole supplier. We have worked closely with our suppliers to develop contingency plans to assure continuity of supply while maintaining high quality and reliability. Due to the FDA's requirements regarding the manufacture of our products, we may not be able to quickly establish additional or replacement sources for certain components or materials. In the event that we are unable to obtain sufficient quantities of raw materials or components on commercially reasonable terms or in a timely manner, our ability to manufacture our products on a timely and cost-competitive basis, may be compromised which may have a material adverse effect on our business, financial condition and results of operations.

We manufacture our direct radiography detectors at our manufacturing facilities in Newark, Delaware and Warstein, Germany. The manufacturing of detectors consists primarily of vapor deposition coatings in clean rooms, microelectronics fabrication, assembly, test, burn-in and quality control. Our manufacturing operations in Germany are focused on the critical process of providing the selenium coatings used in our detectors. We rely on one or only a limited number of suppliers for key components or subassemblies for our detectors. In particular, we have only a limited number of suppliers for our thin-film transistors (TFT). The manufacturing of our direct radiography detectors is highly complex requiring precision, assembly and process control. Product design changes and process improvements, along with new capital equipment have allowed us to increase our production rates while reducing scrap and improving yields.

We manufacture our mammography and breast biopsy systems at our manufacturing facilities in Danbury, Connecticut. We manufacture our R2 Cad line of products, our osteoporosis assessment and our mini C-arm imaging systems at our headquarters in Bedford, Massachusetts. We continue to develop our software for our CAD products at our R2 Santa Clara, California facility.

Suros, a company we acquired in July 2006, specializes in breast biopsy devices. The Suros system control consoles are manufactured by a third party, with quality control performed by our employees. The piece parts related to the disposable device are outsourced and then assembled at our facility in Indianapolis, Indiana, where they are also tested and packaged. We rely on one or a limited number of suppliers for key components of the Suros console and devices, including certain cannulas, plastic components and tubing.

Exhibit 27

Description

The Contura™ MLB Applicator consists of a multi-lumen catheter attached to an inflatable spherical balloon (Figure 1). Lumens are provided for attachment to commercially available HDR (High Dose Rate) remote afterloader equipment for passage of the radiation source delivery wire. Five radiation source wire lumens are provided; one central lumen located along the long axis of the Applicator and four curved lumens symmetrically offset from the central lumen. A removable stiffening stylet is positioned in the central lumen. Two proximal ports are also provided with Luer-type connectors for balloon inflation/deflation and for application of intracavitary vacuum.

The Contura™ MLB accessories provided for introduction and deployment include: trocar with split sheath, drainage catheter, three, 30 ml and one, 10 ml inflation syringes, #11 scalpel, contrast media tray, radiation lumen caps and labels (Figure 2).

Afterloader compatibility:
Model B001-45 - VariSource 200, VariSource ID and Nucletron HDR afterloaders.
Model B011-45 - GammaMedPlus afterloader (Cannot be used with GammaMed 12i)

Warning: The safety and effectiveness of the SenoRx Applicator as a replacement for whole breast irradiation in the treatment of breast cancer has not been established.

Indications for Use

The Contura™ MLB Applicator is intended to provide brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer.

Contraindications

- The Applicator is not intended for use in cavities that are too small, too large and/or of shapes unable to conform to an approximately spherical, 4 to 5 cm diameter SenoRx balloon.
- The Applicator is not intended for use in patients with unusual anatomy including a highly curved rib structure and/or unequal amounts of tissue surrounding the cavity that may cause the SenoRx balloon to be asymmetrical.

Warnings

- Use caution when positioning the trocar tip near the chest wall or skin margin to avoid unintended tissue damage.
- Do not fill the Applicator with more than 58 ml of fluid as overfilling may result in balloon rupture and/or device failure.
- The Applicator must be pre-tested before implantation. Do not use the balloon if it is not approximately spherical and/or any leakage is detected.
- The breast cavity must be imaged before implantation to insure the Applicator will fit appropriately. Do not use if the cavity is too small or if a skin surface to balloon surface distance of less than 5 mm will result.
- To insure appropriate treatment dose distribution, the Applicator must be imaged prior to delivering each fraction of radiation to confirm correct position, balloon volume, skin spacing and conformance.
- If excessive resistance is encountered when attempting to remove the Applicator from the patient, surgical removal is recommended.

- Contrast media concentrations of less than 10% are recommended to prevent dose attenuation.
- Non-ionic contrast media is recommended for patients who are allergic to iodine-based agents.

Precautions

- The Applicator must be used only by physicians trained in catheter implantation, radiation treatment planning and delivery.
- Metal vascular and marking clips should not be used during the lumpectomy procedure to prevent potential abrasion or puncture of the Contura™ balloon. Care should also be taken to direct suture knots and tails away from the cavity and whenever possible position tissue between the potential balloon surface and the tails.
- Store the SenoRx Applicator at room temperature (20 to 25°C).
- Care must be taken when handling and manipulating the Contura™ balloon to prevent damage and foreign material contamination of the balloon surface.
- A scalpel should be used to incise the skin prior to inserting the trocar tip.
- Do not inject fluids into the Vacuum Port.
- Replace Luer caps and radiation lumen caps after use.
- Only clinical personnel trained in the operation of HDR afterloaders should deliver radiation using the Applicator.
- Verify that the appropriate afterloader connectors are available and function with the Applicator prior to treatment.
- Be sure that the Applicator is as straight as possible and free of sharp bends and kinks prior to connecting to the HDR afterloader.
- Inspect package before use. Discard if seal is compromised or packaging is damaged.

Complications

Complications that may be associated with the use of the Contura™ MLB Applicator are the same as those associated with the use of similar devices. These may include: erythema, catheter site drainage, breast pain, ecchymosis, breast fibrosis, telangiectasia, breast induration, breast seroma, breast edema, dry desquamation, dry skin, skin discoloration, parasthesia, axilllary pain, fatigue, pruritis, breast retraction, nausea, skin irritation, moist desquamation, hematoma, rash, asymptomatic fat necrosis, breast infection, breast blister and lymphedema.

How Supplied

The Contura™ MLB Applicator and accessories are provided sterile and are intended for single patient use only.

Directions For Use

- **Placement** - Refer to Figures 1 & 2

1. Use ultrasound to identify the lumpectomy cavity.
2. Open the Contura™ MLB Applicator sterile package and remove the Applicator (A) and one 30 ml Syringe (B). Remove the Inflation Port Luer Cap (C) and inject 58 ml of sterile saline into the Applicator and inspect for leaks and spherical symmetry. Discard Applicator if defective. Holding the Applicator by the connectors, with the balloon hanging vertically, completely withdraw the saline from balloon.
3. Prepare a maximum 5% contrast media/sterile saline solution in the Tray (D) provided.
4. Determine the desired point on the breast surface for the insertion of the Applicator. Inject appropriate anesthetic to the skin and pathway to the lumpectomy cavity. Make a skin incision with the scalpel at the insertion point of sufficient length to fully insert the Trocar (F) tip. Dilate the skin incision, if desired. Advance the Trocar with Split Sheath (G) into the cavity. Remove the Trocar.
5. Attach a 30 ml syringe to the Drainage Catheter (H) and drain any fluids within the cavity by inserting the Drainage Catheter through the Split Sheath and suctioning. Remove the Drainage Catheter.
6. Insert the Applicator through the Split Sheath into the cavity. Remove the Sheath.
7. Align the Radiopaque Line (I) on the catheter shaft with the skin incision.
8. Remove the stiffening Stylet (J) from the Central Source Lumen (K). Attach a red radiation source lumen Cap (L).
9. Using the syringes provided, inflate the Applicator balloon with the contrast media solution to the desired fill volume. Purge any air from the fill syringes before attaching them to the Applicator.

Desired balloon diameter	Approximate balloon fill volume
4 cm	33 ml
5 cm	58 ml

10. Replace the Luer Cap on to the Inflation Port (M).
11. Use ultrasound to confirm appropriate placement, volume and cavity conformance. Fluid and air surrounding the Applicator balloon may be aspirated with a 30 ml Syringe attached to the white Vacuum Port (N). The volume of the balloon may be adjusted through the blue Inflation Port (M). Replace Luer Caps when finished.
12. Confirm that the radiopaque line is aligned with the skin incision.
13. Apply a surgical dressing to the exit site with the catheter positioned to minimize bending.
14. Record the final balloon fill volume on the Labels provided and attach to the patient's chart.

- **Radiation Delivery** - Refer to Figure 3

1. CT imaging should be used in conjunction with commercially available treatment planning software to determine the appropriate source lumens, source dwell positions and dwell times for optimized radiation delivery of a prescribed dose to the targeted treatment volume.
2. Note the orientation of the Contura™ MLB Applicator with respect to the radiopaque line on the catheter shaft. Verify correct Applicator orientation, balloon position, balloon volume, skin spacing and conformance using imaging prior to delivery of each fraction of radiation. Adjust if necessary.
3. The Applicator red-capped, radiation source wire lumens are numbered '1', '2', '3', '4' and '5' and positioned as shown in Figure 3. Lumen number '1' corresponds to the offset lumen closest and parallel to the longitudinal radiopaque line (M) along the outside of the catheter. Lumen number '5' corresponds to the central lumen. Remove the red caps and use commercially available connectors to attach the source lumens to the afterloader.

Note: When using the GammaMedPlus Afterloader, the radiation source lumens of the B011-45 Applicator must first be trimmed to length using the GammaMed length cutting gauge.

4. After each treatment replace the red caps.

- **REMOVAL**

1. Remove the Contura™ MLB Applicator by first attaching a syringe to the blue Inflation Port and deflating the balloon.

   Note: If difficulty is encountered deflating balloon with syringe:

   1) Re-attach syringe and securely rotate clockwise to completely activate the valve. If the balloon, still does not deflate, then
   2) Cut the blue Inflation Port tubing. The saline/contrast contents of the balloon will now drain from the end of the cut tubing

2. Rotate and withdraw (unscrew) the Applicator from the cavity.

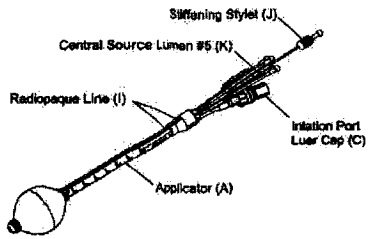

Figure 1: SENORX APPLICATOR

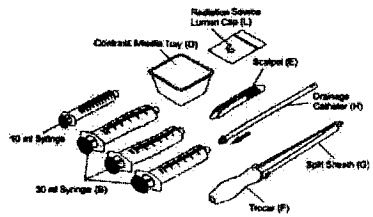

Figure 2: ACCESSORIES

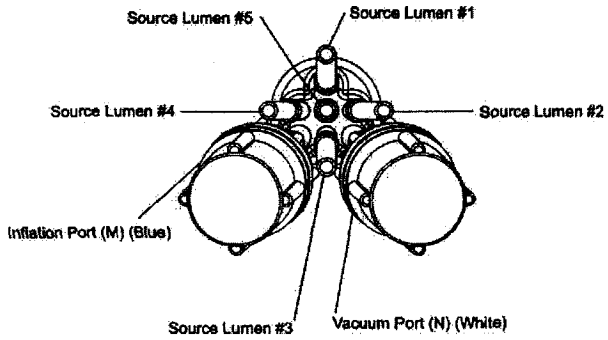

Figure 3: SOURCE WIRE LUMEN ORIENTATION

This product is covered by one or more of the following U.S. Patents: 6,923,754; 6,955,641; 7,241,178. Other domestic and foreign patents pending.

EXPLANATION OF SYMBOLS ON THE PACKAGE

REF	Catalogue Number
	Use by Date
LOT	Lot Number
CONT	Contents
STERILE R	Sterile (Gamma radiation)
	Attention, See Instructions for Use
	Do Not Reuse
	Upper Temperature Limit
	Keep away from sunlight
	Keep dry

SenoRx Inc.
Aliso Viejo, California
USA

Contura™ Multi-Lumen Balloon • MLB

MULTI-LUMEN BALLOON SOURCE APPLICATOR FOR BRACHYTHERAPY

INSTRUCTIONS FOR USE

MODELS

B001-45
B011-45

Caution: **Federal (USA) law restricts this device to sale by or on the order of a physician.**

SENORX

IU0093 Rev. 6
November 2007/ECO 4022

Exhibit 29

HOLOGIC INC (HOLX)

35 CROSBY DRIVE
BEDFORD, MA 01730
781. 999.7300
http://www.hologic.com

10-Q/A

AMENDMENT #1
Filed on 02/12/2008 - Period: 12/29/2007
File Number 000-18281

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10−Q/A
(Amendment No. 1)

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended December 29, 2007

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission File Number: 0−18281

Hologic, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**04−2902449**
(State of incorporation)	**(I.R.S. Employer Identification No.)**
35 Crosby Drive, Bedford, Massachusetts	**01730**
(Address of principal executive offices)	**(Zip Code)**

(781) 999−7300
(Registrant's telephone number, including area code)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non−accelerated filer or a smaller reporting company. See definition of "accelerated filer," "large accelerated filer" and "smaller reporting company" in Rule 12b−2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non−accelerated filer ☐ Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b−2 of the Exchange Act.) Yes ☐ No ☒

As of February 5, 2008, 127,767,649 shares of the registrant's Common Stock, $.01 par value, were outstanding.

HOLOGIC, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Unaudited) – Continued
(In thousands, except per share data)

(b) Acquisition of BioLucent, Inc.

On September 18, 2007 the Company completed the acquisition of BioLucent, Inc. ("BioLucent") pursuant to a definitive agreement dated June 20, 2007. The results of operations for BioLucent have been included in the Company's consolidated financial statements from the date of acquisition as part of its Breast Health business segment. The Company has concluded that the acquisition of BioLucent does not represent a material business combination and therefore no pro forma financial information has been provided herein.

BioLucent, previously located in Aliso Viejo, California, develops, markets and sells MammoPad® breast cushions to decrease the discomfort associated with mammography. Prior to the acquisition, BioLucent's primary research and development efforts were directed at its brachytherapy business which was focused on breast cancer therapy. Prior to the acquisition, BioLucent spun–off its brachytherapy technology and business to the holders of BioLucent's outstanding shares of capital stock. As a result, the Company only acquired BioLucent's MammoPad cushion business and related assets. The Company invested $1,000 directly in the spun–off brachytherapy business in exchange for shares of preferred stock issued by the new business.

The aggregate purchase price for BioLucent was approximately $73,200 (subject to adjustment) consisting of approximately $6,800 in cash and 1,157 shares of Hologic Common Stock valued at approximately $63,200, debt assumed and paid off of approximately $1,600 and approximately $1,600 for acquisition related fees and expenses. The Company determined the fair value of the shares issued in connection with the acquisition in accordance with EITF Issue No. 99–12, *Determination of the Measurement Date for the Market Price of Acquirer Securities Issued in a Purchase Business Combination.*

The acquisition also provides for up to two annual earn–out payments not to exceed $15,000 in the aggregate based on BioLucent's achievement of certain revenue targets. The Company has considered the provision of EITF Issue No. 95–8, *Accounting for Contingent Consideration Paid to the Shareholders of an Acquired Enterprise in a Purchase Business Combination*, and concluded that this contingent consideration will represent additional purchase price. As a result, goodwill will be increased by the amount of the additional consideration, if any, when it becomes due and payable. As of December 29, 2007, the Company has not recorded any amounts for this potential earn–out. The allocation of the purchase price is based upon preliminary estimates of the fair value of assets acquired and liabilities assumed as of September 18, 2007. The Company is in the process of gathering information to finalize its valuation of certain assets and liabilities. The purchase price allocation is preliminary and will be finalized once the Company has all necessary information to complete its estimate, but generally no later than one year from the date of acquisition. The components and initial allocation of the purchase price, consists of the following approximate amounts:

Net tangible assets acquired as of September 18, 2007	$ 3,400
Developed technology and know–how	12,300
Customer relationship	17,000
Trade name	2,800
Deferred income tax liabilities, net	(9,500)
Goodwill	47,200
Estimated Purchase Price	$73,200

As part of the purchase price allocation, all intangible assets that were a part of the acquisition were identified and valued. It was determined that only customer relationship, trade name and developed technology and know how had separately identifiable values. The fair value of these intangible assets was determined through the application of the income approach. Customer relationship represents a large customer base that is expected to purchase the disposable MammoPad product on a regular basis. Trade name represents the BioLucent product name that the Company intends to continue to use. Developed technology and know–how represents currently marketable purchased products that the Company continues to sell as well as utilize to enhance and incorporate into the Company's existing products. The Company reduced goodwill related to the BioLucent acquisition in the amount of approximately $600 during the three months ended December 29, 2007. The reduction was primarily related to a change in the preliminary valuation of certain liabilities acquired based on information received during the period.